=> fil hcap

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FILE COVERS 1907 - 27 Nov 2004 VOL 141 ISS 23
FILE LAST UPDATED: 26 Nov 2004 (20041126/ED)

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=> fil medlin

FILE 'MEDLINE' ENTERED AT 12:01:56 ON 27 NOV 2004

FILE LAST UPDATED: 26 NOV 2004 (20041126/UP). FILE COVERS 1950 TO DATE.

On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD for details.

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description of changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil biosis
A SUBSCRIBER PRICE 0.00 -11.20

FILE 'BIOSIS' ENTERED AT 12:01:58 ON 27 NOV 2004

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 24 November 2004 (20041124/ED)

FILE RELOADED: 19 October 2003.

=> fil jicst

FILE 'JICST-EPLUS' ENTERED AT 12:02:02 ON 27 NOV 2004
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FILE COVERS 1985 TO 22 NOV 2004 (20041122/ED)

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=> fil pascal

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FILE LAST UPDATED: 22 NOV 2004 <20041122/UP>
FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE
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=> fil caba

FILE 'CABA' ENTERED AT 12:02:10 ON 27 NOV 2004
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FILE COVERS 1973 TO 8 Nov 2004 (20041108/ED)

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=> fil embase

FILE 'EMBASE' ENTERED AT 12:02:14 ON 27 NOV 2004
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FILE COVERS 1974 TO 19 Nov 2004 (20041119/ED)

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This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> fil confsci

FILE 'CONFSCI' ENTERED AT 12:02:18 ON 27 NOV 2004
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FILE COVERS 1973 TO 18 Nov 2004 (20041118/ED)

=> fil wpix

FILE 'WPIX' ENTERED AT 12:02:21 ON 27 NOV 2004
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FILE LAST UPDATED: 25 NOV 2004 <20041125/UP>
MOST RECENT DERWENT UPDATE: 200476 <200476/DW>

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>>> SMILES and ISOSMILES strings are no longer available as
    Derwent Chemistry Resource display fields  <<<

=> file stnguide

FILE 'STNGUIDE' ENTERED AT 12:02:23 ON 27 NOV 2004
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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Nov 19, 2004 (20041119/UP).

=> d que l11
L4  (      6104)SEA FILE=HCAPLUS ABB=ON  PLU=ON  YAMASHITA, T?/AU
L5  (       206)SEA FILE=HCAPLUS ABB=ON  PLU=ON  NARA, H?/AU
L6  (       583)SEA FILE=HCAPLUS ABB=ON  PLU=ON  TAKIZAWA, M?/AU
L7  (      2162)SEA FILE=HCAPLUS ABB=ON  PLU=ON  YOSHIMURA, K?/AU
L8  (        49)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L4 OR L5 OR L6 OR L7) AND
                  ?THIOL?
L9  (         5)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 AND ?PYRROL?
L10 (        10)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 AND ?TAKEDA?/CS,SO,PA
L11          11 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L9 OR L10

 (FILE 'MEDLINE, BIOSIS, JICST-EPLUS, PASCAL, CABA, EMBASE, CONFSCI, WPIX'
    ENTERED AT 11:52:23 ON 27 NOV 2004)

=> d que l62
L53       17677 SEA YAMASHITA, T?/AU
L54         479 SEA NARA, H?/AU
L55        1745 SEA TAKIZAWA, M?/AU
L56        6636 SEA YOSHIMURA, K?/AU
L57       64888 SEA METALLOPROTEAS? OR ?METALLOPROTEAS? OR MMP?
L58          63 SEA (L53 OR L54 OR L55 OR L56) AND L57
L59          31 DUP REM L58 (32 DUPLICATES REMOVED)
L60           7 SEA L59 AND (?THIO? OR THIO?)
L61          10 SEA L59 AND (?TAKEDA? OR TAKEDA?)/SO,CS,PA
L62          12 SEA L60 OR L61
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=> dup rem l11 l62

FILE 'HCAPLUS' ENTERED AT 12:03:08 ON 27 NOV 2004
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FILE 'MEDLINE' ENTERED AT 12:03:08 ON 27 NOV 2004

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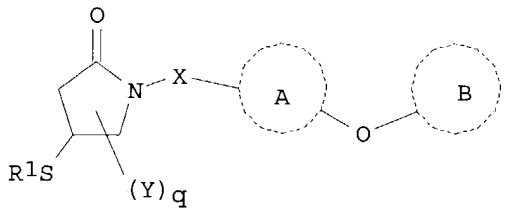
FILE 'WPIX' ENTERED AT 12:03:08 ON 27 NOV 2004
COPYRIGHT (C) 2004 THE THOMSON CORPORATION
PROCESSING COMPLETED FOR L11
PROCESSING COMPLETED FOR L62
L63 20 DUP REM L11 L62 (3 DUPLICATES REMOVED)
ANSWERS '1-11' FROM FILE HCAPLUS
ANSWERS '12-13' FROM FILE MEDLINE
ANSWER '14' FROM FILE BIOSIS
ANSWER '15' FROM FILE EMBASE
ANSWERS '16-20' FROM FILE WPIX

=> d ibib abs ed

L63 ANSWER 1 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2003:875277 HCAPLUS
DOCUMENT NUMBER: 139:364833
TITLE: Preparation of heterocyclic **thiol** compounds as matrix metalloprotease inhibitors
INVENTOR(S): Kajino, Masahiro; **Takizawa, Masayuki**; Notoya, Kohei; **Nara, Hiroshi**; Ikemoto, Tomomi; Nishiguchi, Atsuko
PATENT ASSIGNEE(S): **Takeda Chemical Industries, Ltd., Japan**
SOURCE: PCT Int. Appl., 116 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003091242	A1	20031106	WO 2003-JP5255	20030424
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
JP 2004002405	A2	20040108	JP 2003-119405	20030424

PRIORITY APPLN. INFO.: JP 2002-126943 A 20020426
OTHER SOURCE(S): MARPAT 139:364833
GI



I

AB The title compds. I [wherein the ring A is a substituted or unsubstituted aromatic heterocycle; the ring B is a substituted or unsubstituted homocycle or heterocycle; R1 is a hydrogen atom, a substituted or unsubstituted hydrocarbon group, an acyl group, a substituted or unsubstituted heterocyclic group or SR2 (R2 is a hydrogen atom, a substituted or unsubstituted hydrocarbon group, an acyl group or a substituted or unsubstituted heterocyclic group); X is a substituted or unsubstituted divalent C1-3 aliphatic hydrocarbon group; Y is a substituted or unsubstituted hydrocarbon group, a halogen atom, a carboxyl group, an acyl group, a substituted or unsubstituted hydroxyl group, a substituted or unsubstituted amino group, SR3 (R3 is a hydrogen atom, a substituted or unsubstituted hydrocarbon group, an acyl group or a substituted or unsubstituted heterocyclic group), an oxo group, a thioxo group, a substituted or unsubstituted imino group, a nitro group or a cyano group; and q is an integer of 0 to 5] are prepared Processes for preparing I are disclosed. One compound of this invention at 1.5 nM gave 67% inhibition of MMP-13. Formulations are given.
ED Entered STN: 07 Nov 2003
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs ed 2-
YOU HAVE REQUESTED DATA FROM 19 ANSWERS - CONTINUE? Y/(N):y

L63 ANSWER 2 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2002:888746 HCAPLUS
DOCUMENT NUMBER: 138:4599
TITLE: Preparation of fused imidazolidine derivatives as inhibitors of cartilage matrix degradation
INVENTOR(S): Funabashi, Yasunori; **Takizawa, Masayuki**; Morimoto, Shinji; Notoya, Kohei
PATENT ASSIGNEE(S): **Takeda Chemical Industries, Ltd., Japan**
SOURCE: PCT Int. Appl., 940 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002092606	A1	20021121	WO 2002-JP4640	20020514
WO 2002092606	C1	20021219		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,
PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

JP 2003034691 A2 20030207 JP 2002-139642 20020515
PRIORITY APPLN. INFO.: JP 2001-144608 A 20010515
OTHER SOURCE(S): MARPAT 138:4599
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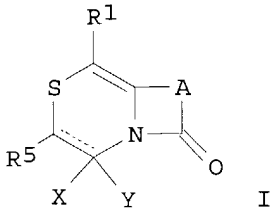

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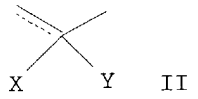

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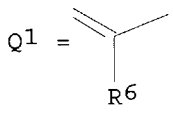

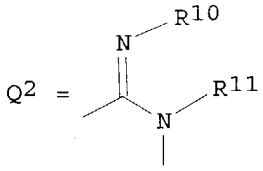

AB The title compds. I [R1 = (S)nR2, etc.; n = 0 - 2; R2 = H, (un)substituted hydrocarbon, etc.; R5 = H, (un)substituted hydrocarbon, etc.; the moiety represented by II in I is Q1, etc.; R6 = H, (un)substituted hydrocarbon, etc.; A = Q2, etc.; R10 = H, ZR15, etc.; Z = SO2, etc.; R15 = (un)substituted hydrocarbon, etc.; R11 = H, (un)substituted hydrocarbon] are prepared A process for preparing I is disclosed. Compds. of this invention in vitro at 0.1 μM gave 20% to 55% inhibition of MMP-13 production Formulations are given.

ED Entered STN: 22 Nov 2002
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L63 ANSWER 3 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2000:210116 HCAPLUS
DOCUMENT NUMBER: 132:251070
TITLE: Preparation and utilization of novel **thiol** derivatives
INVENTOR(S): **Yamashita, Toshiro; Nara, Hiroshi; Takizawa, Masayuki; Yoshimura, Koji**
PATENT ASSIGNEE(S): **Takeda Chemical Industries, Ltd., Japan**
SOURCE: PCT Int. Appl., 261 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000017162	A1	20000330	WO 1999-JP5103	19990920
W: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2344412	AA	20000330	CA 1999-2344412	19990920
AU 9956537	A1	20000410	AU 1999-56537	19990920
JP 2000159747	A2	20000613	JP 1999-266295	19990920
EP 1132379	A1	20010912	EP 1999-943412	19990920
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6420415	B1	20020716	US 2001-787623	20010320
US 2003078253	A1	20030424	US 2002-161289	20020603
US 6699881	B2	20040302		
US 2004157894	A1	20040812	US 2004-757325	20040113
PRIORITY APPLN. INFO.:			JP 1998-266037 A	19980921
			WO 1999-JP5103 W	19990920
			US 2001-787623 A3	20010320
			US 2002-161289 A3	20020603

OTHER SOURCE(S): MARPAT 132:251070

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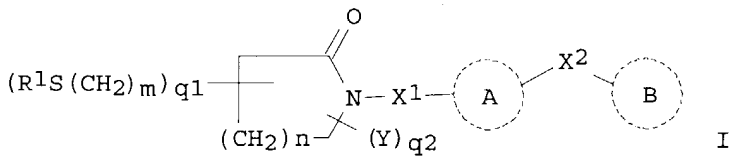

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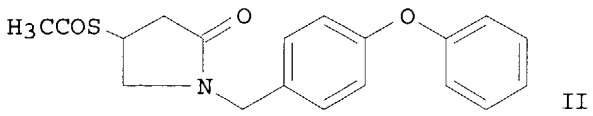

II

AB Title compds [I; wherein the rings A and B represent each an optionally substituted homocycle or heterocycle, etc.; R1s are the same or different and each represents hydrogen, optionally substituted hydrocarbyl, acyl, etc.; X1 represents a bond, optionally substituted divalent aliphatic hydrocarbyl, etc.; X2 represents a bond, optionally substituted divalent aliphatic hydrocarbyl, O, etc.; Ys are the same or different and each represents hydrogen, optionally substituted hydrocarbyl, oxo, etc.; m is 0 or 1; n is an integer of 1 to 3; q1 is an integer of 1 to 2n+4; and q2 is an integer of 0 to 2n+3, provided that q1+q2 is 2n+4], stereoisomers, and salts thereof are prepared and tested as matrix metalloprotease inhibitors

and are useful as drugs. The title compound (R)-II was prepared and tested.
ED Entered STN: 31 Mar 2000
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L63 ANSWER 4 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:747795 HCAPLUS
DOCUMENT NUMBER: 135:303882
TITLE: Preparation of thienobenzisoxazoles and thienoindazoles for prevention and treatment of bone or articular diseases
INVENTOR(S): Yasuma, Tsuneo; Mori, Akira; Kawase, Masahiro; **Takizawa, Masayuki**; Miki, Shokyo; Takeda, Mitsuhiro
PATENT ASSIGNEE(S): **Takeda Chemical Industries, Ltd., Japan**
SOURCE: PCT Int. Appl., 486 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2001074823	A2	20011011	WO 2001-JP2614		20010329
WO 2001074823	A3	20020207			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2400858	AA	20011011	CA 2001-2400858		20010329
JP 2002255971	A2	20020911	JP 2001-94980		20010329
EP 1268486	A2	20030102	EP 2001-917582		20010329
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
US 2003158245	A1	20030821	US 2002-204472		20020821
PRIORITY APPLN. INFO.:			JP 2000-101373	A	20000331
			JP 2000-101374	A	20000331
			JP 2000-392843	A	20001225
			WO 2001-JP2614	W	20010329

OTHER SOURCE(S): MARPAT 135:303882
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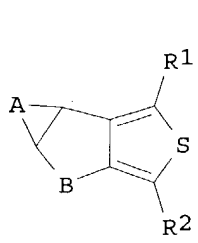

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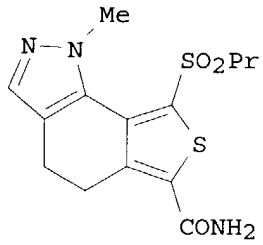

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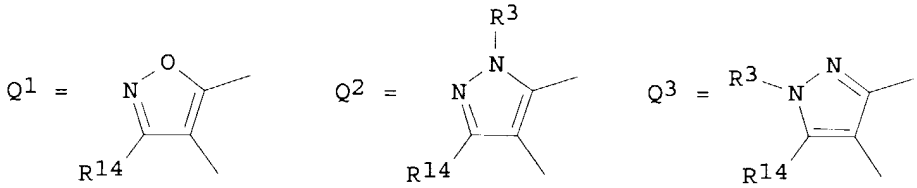


AB The title fused thiophene derivs. I [wherein R1 = (un)substituted hydrocarbon, heterocyclic, sulfinyl, sulfonyl, hydroxyl, **thiol**, or amino; R2 = CN, CHO, CHS, etc.; ring A = Q1, Q2, or Q3; R3 = H or (un)substituted hydrocarbon, heterocyclic, hydroxyl, amino, sulfonyl, or acyl; R14 = H, halo, (un)substituted hydrocarbon or heterocyclic group, etc.; ring B = (un)substituted 5- to 7-membered hydrocarbon ring] and their intermediates were prepared using industrially advantageous processes as prophylactic and therapeutic drugs for bone or articular diseases. For example, cycloaddn. of MeNHNH2•H2O with 5-diethoxymethyl-3-propylsulfanyl-4-oxo-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxylic acid Et ester (preparation given) using HCl in EtOH (80%), followed by saponification (93%), amidation (79%), and oxidation with m-chloroperbenzoic acid (42%), gave II. The latter enhanced chondromodulin-I (ChM-I) mRNA expression in ATDC5, a substrain derived from mouse teratocarcinoma cell line AT805, with ChM-I band d. of 10-6 M.

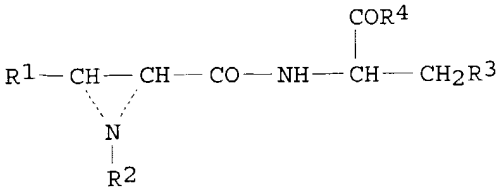
ED Entered STN: 12 Oct 2001

L63 ANSWER 5 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:594557 HCAPLUS
DOCUMENT NUMBER: 127:220996
TITLE: Preparation of aziridine dicarboxylic acid derivatives as cathepsin L inhibitors
INVENTOR(S): Tsuboya, Shigetoshi; **Takizawa, Masayuki**; Hattori, Masahiko; Shirasaki, Mikio
PATENT ASSIGNEE(S): **Takeda Chemical Industries, Ltd., Japan**
SOURCE: Jpn. Kokai Tokkyo Koho, 22 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 09221470	A2	19970826	JP 1996-302886	19961114
PRIORITY APPLN. INFO.:			JP 1995-323374	19951212

OTHER SOURCE(S): MARPAT 127:220996
GI



I

AB The title compds. [I; R1 = (Et esterified) carboxylyl; R2 = H, Me, Et; R3 = Ph, naphthyl; R4 = MeO(CH2)3NH, Ph(CH2)2NH, etc.] are prepared I are useful as cathepsin L and **thiol** protease inhibitors and antiinflammatory agents for prevention and treatment of myocardiopathy, osteoporosis and related bone diseases. Thus, aziridine derivative I (R1 = EtO2C, R2 = H, R3 = Ph, R4 = NH(CH2)3OMe) (preparation given) was treated with aqueous NaOH in MeOH to give 87% I (R1 = CO2Na, R2-R4 = same as above), which showed IC50 of 1.8 ng/mL against cathepsin L. A capsule formulation containing I was prepared
ED Entered STN: 17 Sep 1997

L63 ANSWER 6 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:210920 HCAPLUS
DOCUMENT NUMBER: 126:198634
TITLE: Interleukin inhibitor TAN-2178 and derivatives manufacture with Streptomyces
INVENTOR(S): Funahashi, Yasunori; Kawamura, Noriaki; **Yoshimura, Koji**; Makino, Haruhiko
PATENT ASSIGNEE(S): **Takeda Chemical Industries Ltd, Japan**
SOURCE: Jpn. Kokai Tokkyo Koho, 32 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 09012595	A2	19970114	JP 1996-107404	19960426
PRIORITY APPLN. INFO.:			JP 1995-104458	19950427

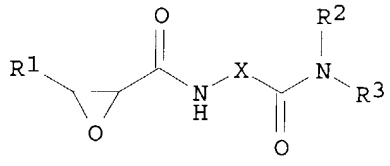
OTHER SOURCE(S): MARPAT 126:198634
AB Interleukin inhibitor TAN-2178 and derivs. R1C(O)CH(CH2R2)C(O)NHC(R3)C(O)CR5(CH2R4)(CH2R6) (I: R1 = C1-6 alkyl; R2 and R4 = OH or substituted OH; R3 = 2-methylpropyl, etc.; R5 = OH; R6 = halogen, substituted **thiol** or **thiol**) are manufactured by culturing I-producing Streptomyces sp. AL-78099 and chemical synthesis. I inhibit the formation and/or biosynthesis of interleukin. Manufacture of TAN-2178 and 31 derivs. were shown. The physiol. and morphol. characteristics of Streptomyces sp. AL-78099 were also given.
ED Entered STN: 02 Apr 1997

L63 ANSWER 7 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:184020 HCAPLUS
DOCUMENT NUMBER: 124:233141
TITLE: Epoxysuccinic acid peptide derivatives, their production, and use for treatment of bone disease and inhibition of **thiol** protease
INVENTOR(S): Tsubotani, Shigetoshi; **Takizawa, Masayuki**;

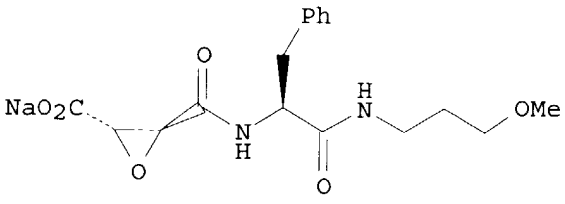
Mizoguchi, Junji
PATENT ASSIGNEE(S): **Takeda Chemical Industries, Ltd., Japan**
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9532954	A1	19951207	WO 1995-JP1004	19950525
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, US, UZ, VN				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2190151	AA	19951207	CA 1995-2190151	19950525
AU 9525376	A1	19951221	AU 1995-25376	19950525
EP 763029	A1	19970319	EP 1995-919635	19950525
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 08104684	A2	19960423	JP 1995-132050	19950530
US 5679708	A	19971021	US 1995-513895	19950905
PRIORITY APPLN. INFO.:			JP 1994-119206	19940531
			JP 1994-186166	19940808
			WO 1995-JP1004	19950525

OTHER SOURCE(S): MARPAT 124:233141
GI



I



II

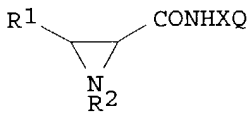
AB The invention relates to compds. I [R1 = optionally esterified or amidated CO2H; X = (un)substituted divalent hydrocarbon residue; R2 = H or (un)substituted hydrocarbon residue; R3 = alkyl which is substituted with a group bonded through O or S(O)n (n = 0, 1, or 2); with proviso that when NHXCO is a Leu residue, R3 ≠ 3-hydroxy-3-methylbutyl nor 4-hydroxy-3-methylbutyl] and salts. I are useful as prophylactic and therapeutic agents for bone diseases (especially osteoporosis), and as inhibitors of **thiol** protease. For example, peptide coupling of H-Phe-OCH2Ph.p-MeC6H4SO3H with (2S,3S)-trans-Et hydrogen epoxysuccinate (77%), followed by hydrogenolytic deprotection (96%), amidation with MeO(CH2)3NH2 (65%), and hydrolysis with aqueous NaOH in MeOH (85%), gave title compound II. In a test against human recombinant cathepsin L in vitro, II

had an IC50 of 3 ng/mL. I also suppressed bone resorption (142-176%) in mice.
ED Entered STN: 30 Mar 1996

L63 ANSWER 8 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:998130 HCAPLUS
DOCUMENT NUMBER: 124:176939
TITLE: Preparation of (aziridinylcarbonyl)amino acid amides as **thiol** protease inhibitors.
INVENTOR(S): Tsubotani, Shigetoshi; **Takizawa, Masayuki**; Shirasaki, Mikio; Mizoguchi, Junji; Shimizu, Yoshiaki
PATENT ASSIGNEE(S): **Takeda Chemical Industries, Ltd., Japan**
SOURCE: PCT Int. Appl., 143 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9528416	A1	19951026	WO 1995-JP718	19950412
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TT, UA, US, UZ, VN				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2187451	AA	19951026	CA 1995-2187451	19950412
AU 9522235	A1	19951110	AU 1995-22235	19950412
EP 753003	A1	19970115	EP 1995-915310	19950412
EP 753003	B1	19990616		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AT 181333	E	19990715	AT 1995-915310	19950412
JP 08183767	A2	19960716	JP 1995-87885	19950413
US 5668128	A	19970916	US 1995-513896	19950905
PRIORITY APPLN. INFO.:			JP 1994-74621	19940413
			JP 1994-269175	19941101
			WO 1995-JP718	19950412

OTHER SOURCE(S): MARPAT 124:176939
GI



I

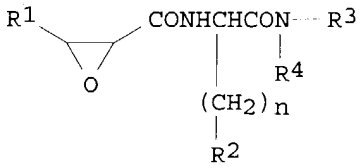
AB Title compds. [I; R1, Q = (esterified or amidated) carboxy; R2 = H, acyl, (substituted) hydrocarbyl; X = (substituted) divalent hydrocarbyl], were prepared Thus, N-[N-[(2S,3S)-3-carboxyaziridine-2-carbonyl]-L-phenylalanyl]-1,4-diaminobutane (II) (solution phase preparation given) inhibited cathepsin L with IC50 = 3 ng/mL, and at 10 μg/mL gave 99% inhibition of parathyroid hormone-enhanced mouse bone resorption. A capsule formulation containing II is given.
ED Entered STN: 22 Dec 1995

L63 ANSWER 9 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:886024 HCAPLUS
DOCUMENT NUMBER: 123:286713
TITLE: Preparation of epoxysuccinic acid-derivative inhibitors of **thiol** proteases for treatment of osteoporosis
INVENTOR(S): Tsubotani, Shigetoshi; **Takizawa, Masayuki**; Shirasaki, Mikio; Fujisawa, Yukio
PATENT ASSIGNEE(S): **Takeda Chemical Industries, Ltd., Japan**
SOURCE: Eur. Pat. Appl., 95 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 655447	A1	19950531	EP 1994-307984	19941028
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
US 5556853	A	19960917	US 1994-330833	19941027
CA 2134627	AA	19950430	CA 1994-2134627	19941028
FI 9405092	A	19950430	FI 1994-5092	19941028
NO 9404121	A	19950502	NO 1994-4121	19941028
AU 9477552	A1	19950518	AU 1994-77552	19941028
CN 1112555	A	19951129	CN 1994-118687	19941028
JP 08104683	A2	19960423	JP 1994-265686	19941028
HU 72319	A2	19960429	HU 1994-3116	19941028
PRIORITY APPLN. INFO.:			JP 1993-272806 A	19931029
			JP 1993-272835 A	19931029
			JP 1994-186165 A	19940808

OTHER SOURCE(S): MARPAT 123:286713
GI



I

AB The title compds. [I; R1 = (un)substituted carboxyl group; R2 = (un)substituted cyclic group; R3 = H, (un)substituted hydrocarbon residue; R4 = (un)substituted hydrocarbon residue with optionally protected amino group, alkenyl; n = 0-6; R3R4N = heterocyclic residue], which are inhibitors of **thiol** proteases such as cathepsin L or B, useful as prophylactic and/or therapeutic agents for bone diseases such as osteoporosis, are prepared and I-containing formulations presented. Thus, N-Z-N'-[N-(2S,3S)-trans-carboxyoxirane-2-carbonyl]-o-fluoro-L-phenylalanyl]-1,4-diaminobutane (sic) was prepared and demonstrated a IC50 of 1 ng/mL against cathepsin L and 14 ng/mL against cathepsin B.
ED Entered STN: 31 Oct 1995

L63 ANSWER 10 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:102698 HCAPLUS
DOCUMENT NUMBER: 114:102698

TITLE: Preparation of saccharoascorbic acid derivatives as antioxidant food additives and synthetic intermediates.

INVENTOR(S): Matsumura, Koichi; Shimizu, Yoshiaki; **Yamashita, Toshiro**; Sugihara, Yoshihiro; Iida, Kouichi

PATENT ASSIGNEE(S): **Takeda Chemical Industries, Ltd., Japan**

SOURCE: Eur. Pat. Appl., 67 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

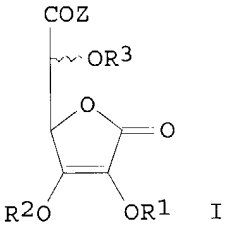
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 381472	A1	19900808	EP 1990-301004	19900131
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL				
CA 2009006	AA	19900731	CA 1990-2009006	19900131
CN 1044655	A	19900815	CN 1990-100429	19900131
JP 02282379	A2	19901119	JP 1990-23400	19900131
JP 02282380	A2	19901119	JP 1990-23401	19900131
JP 02288872	A2	19901128	JP 1990-23402	19900131
US 5043459	A	19910827	US 1990-473154	19900131
PRIORITY APPLN. INFO.:			JP 1989-23481 A	19890131
			JP 1989-23482 A	19890131
			JP 1989-23483 A	19890131

OTHER SOURCE(S): MARPAT 114:102698

GI



I

AB The title compds. [I; Z = NR4R5, SR6, OR7; R4,R5,R6,R7 = C1-24 hydrocarbyl; or R4R5 = (CH2)n; n = 4-7; R1,R2,R3 = H, C1-18 acyl, C1-24 hydrocarbyl; provided that when Z = OR7, R1 ≠ R2 and R3 = H], also useful as intermediates for dichiral compds., e.g. liquid crystals, and antithrombotics, are prepared, e.g. by reaction of I(Z = OH; R2,R2 = protective group R3 = same as above) with HNR4R5 or R6SH. Thus, treatment of 5-O-acetyl-2,3-di-O-benzyl-β-glucosaccharoascorbic acid (II) with PCl5 in Cl2CH2 and amidation of the resulting acid chloride with n-C10H21NH2 in Cl2CH2 gave 75.8% n-decylamide of II which was deacetylated with 2N aqueous H2SO4-MeCN in 63.3% yield and then hydrogenolyzed over 5% Pd/C in EtOAc to give 74.8% n-decylamide of D-glucosaccharoascorbic acid (III). III had the same level of reducing activity as that of D-glucosaccharoascorbic acid. A total of 71 I were prepared

ED Entered STN: 23 Mar 1991

L63 ANSWER 11 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1987:67102 HCAPLUS

DOCUMENT NUMBER: 106:67102

TITLE: Lactams and **thiolactams** as antiinflammatory

agents
INVENTOR(S): Imai, Naohiro; Fuse, Yoshihide; Katsumi, Ikuo; Yamashita, Katsuji; Hidaka, Takayasu; Hosoe, Kazunori; Ariki, Yutaka; **Yamashita, Toshiaki**; Watanabe, Kiyoshi
PATENT ASSIGNEE(S): Kanegafuchi Chemical Industry Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 14 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 61218571	A2	19860929	JP 1985-58971	19850323
JP 06023194	B4	19940330		
PRIORITY APPLN. INFO.:			JP 1985-58971	19850323

GI For diagram(s), see printed CA Issue.
AB (Thio)lactams I (R1 = H, C1-8 alkyl, PhCH2, acyl; R2 = H, C1-6 alkyl; R3, R4 = H, R3R4 = bond, R5 = H, C1-3 alkyl, acyl; X = O, S; n = 2-5), effective antiinflammatory agents at 50 mg/kg p.o. in rats, are prepared Thus, a solution of 8.19 g aldehyde II and 3.56 g **pyrrolidone** III in THF was added to a suspension of 3.36 g 60 weight% oily NaH in THF under N and cooling, stirred at room temperature, and hydrolyzed to give 47% I (R1 = R2 = R5 = H, R3R4 = bond, X = O, n = 2).
ED Entered STN: 07 Mar 1987

L63 ANSWER 12 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2000226992 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10765925
TITLE: Production of tissue inhibitor of metalloproteinases 3 is selectively enhanced by calcium pentosan polysulfate in human rheumatoid synovial fibroblasts.
AUTHOR: **Takizawa M**; Ohuchi E; Yamanaka H; Nakamura H; Ikeda E; Ghosh P; Okada Y
CORPORATE SOURCE: Keio University, and Grelan Pharmaceutical Co., Tokyo, Japan.
SOURCE: Arthritis and rheumatism, (2000 Apr) 43 (4) 812-20.
Journal code: 0370605. ISSN: 0004-3591.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000525
Last Updated on STN: 20000525
Entered Medline: 20000518
AB OBJECTIVE: To determine the effects of calcium pentosan polysulfate (CaPPS) on the production of matrix metalloproteinases (**MMPs**) and their endogenous inhibitors, tissue inhibitors of metalloproteinases (TIMP), in cultures of rheumatoid synovial fibroblasts. METHODS: The production of **MMP**-1, -2, -3, -7, -8, -9, and -13 and of TIMP-1, -2, -3, and -4 in cultured rheumatoid synovial fibroblasts treated with 0.1, 1, and 10 microg/ml CaPPS in the presence and absence of 100 units/ml interleukin-1alpha (IL-1alpha) was examined by a sandwich enzyme immunoassay system and/or immunoblotting. The messenger RNA (mRNA) expression of TIMP-3 and membrane type 1 **MMP** was determined by Northern blotting, and the cells expressing TIMP-3 gene in rheumatoid synovium were identified by in situ hybridization. The synthesis and

secretion of TIMP-3 protein were monitored by pulse-chase experiments. TIMP-3 was immunolocalized in untreated or CaPPS-treated rheumatoid synovial fibroblasts and synovium using an avidin-biotin-peroxidase complex method. RESULTS: Treatment of cultured rheumatoid synovial fibroblasts with CaPPS resulted in a dose-dependent increase in the production of TIMP-3 in both cell lysates and media from the treated cells. However, CaPPS did not affect the levels of the other **MMPs** or TIMPs examined. The production of TIMP-3 was further enhanced in the cells treated with both IL-1alpha and CaPPS. Immunohistochemistry confirmed the enhanced production of TIMP-3 by cells exposed to CaPPS. The mRNA level of TIMP-3 increased 3.4-fold by treating rheumatoid synovial fibroblasts with IL-1alpha, but CaPPS itself did not alter the expression levels in the IL-1alpha-treated or -untreated cells. Pulse-chase studies demonstrated that translation for TIMP-3 protein was enhanced by CaPPS treatment. In situ hybridization and immunohistochemistry indicated that TIMP-3 was expressed mainly in the hyperplastic lining cells of rheumatoid synovium, and that the production of this protein by these immunoreactive lining cells was significantly increased by treatment with CaPPS. CONCLUSION: The present study is the first to demonstrate that the new antiarthritic drug, CaPPS, selectively enhanced TIMP-3 production at the posttranscription level in cultured rheumatoid synovial fibroblasts and in the lining cells of rheumatoid synovium. By this mechanism, CaPPS may be able to modulate joint tissue destruction in rheumatoid arthritis.

ED Entered STN: 20000525
Last Updated on STN: 20000525
Entered Medline: 20000518

L63 ANSWER 13 OF 20 MEDLINE on STN
ACCESSION NUMBER: 88299969 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2457066
TITLE: Oligo-2',5'-adenylate synthetase activity in K562 cell lines persistently infected with measles or mumps virus.
AUTHOR: Fujii N; Oguma K; Kimura K; **Yamashita T**; Ishida S; Fujinaga K; Yashiki T
CORPORATE SOURCE: Department of Microbiology, Sapporo, Medical College, Japan.
SOURCE: Journal of general virology, (1988 Aug) 69 (Pt 8) 2085-91. Journal code: 0077340. ISSN: 0022-1317.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198809
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19880916

AB Fluctuation of oligo-2',5'-adenylate synthetase (2-5AS) activity was examined in K562 cells infected with vaccine strains of measles virus (strains AIK-C and CAM-70) and mumps virus (strains Torii and Miyahara). Persistent infection was easily established in the mumps virus-infected cells without significant cytolysis or cell killing. In contrast, most of the cells infected with measles virus were killed by extensive cytolysis within 3 to 4 days. The small number of cells that did survive became persistently infected. That these persistently infected cells carried a virus antigen was confirmed by fluorescein **isothiocyanate** -labelled anti-measles virus rabbit antiserum and anti-mumps virus rabbit antiserum. The cells produced infectious progeny virus as well as interferon (IFN). Little induction of 2-5AS activity by IFN was demonstrated during the early stages of infection by these viruses.

Similar results were observed in some of the persistently infected cells but not, however, K-CMP cells (K562 cells persistently infected with CAM-70) or K-**MMP** cells (K562 cells persistently infected with Miyahara). Failure to induce 2-5AS activity was unchanged in cells cultured for more than 6 months. The decrease of 2-5AS activity observed in K-MTP cells (K562 cells persistently infected with Torii) was the result of suppression of transcription of 2-5AS mRNA. On the other hand, a normal level of mRNA was found in K-AKP cells (K562 cells persistently infected with AIK-C). Therefore, it is suggested that the decrease of 2-5AS activity in K-AKP cells may be due to a failure to translate 2-5AS mRNA.

ED Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19880916

L63 ANSWER 14 OF 20 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2002:475379 BIOSIS
DOCUMENT NUMBER: PREV200200475379
TITLE: **Thiol** compounds, their production and use.
AUTHOR(S): **Yamashita, Toshiro** [Inventor, Reprint author]; **Nara, Hiroshi** [Inventor]; **Takizawa, Masayuki** [Inventor]; **Yoshimura, Koji** [Inventor]
CORPORATE SOURCE: Tsukuba, Japan
ASSIGNEE: **Takeda Chemical Industries, Ltd., Osaka, Japan**
PATENT INFORMATION: US 6420415 July 16, 2002
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (July 16, 2002) Vol. 1260, No. 3. http://www.uspto.gov/web/menu/patdata.html. e-file. CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 11 Sep 2002
Last Updated on STN: 11 Sep 2002

AB Compounds represented by general formula (1) or salts thereof which have a matrix **metalloprotease** inhibitory activity and are useful as drugs, wherein the rings A and B represent each an optionally substituted homocycle or heterocycle, etc.; R1 s are the same or different and each represents hydrogen, optionally substituted hydrocarbyl, acyl, etc.; X1 represents a bond, optionally substituted divalent aliphatic hydrocarbyl, etc.; X2 represents a bond, optionally substituted divalent aliphatic hydrocarbyl, --O--, etc.; Ys are the same or different represents hydrogen, optionally substituted hydrocarbyl, oxo, etc.; m is 0 or 1; n is an integer of 1 to 3; q1 is an integer of 1 to 2n+4; and q2 is an integer of 0 to 2n+3, provided that q1 +q2 is 2n+4. ##STR1##

ED Entered STN: 11 Sep 2002
Last Updated on STN: 11 Sep 2002

L63 ANSWER 15 OF 20 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001351101 EMBASE
TITLE: Expression of membrane-type matrix metalloproteinases in synovial tissue from patients with rheumatoid arthritis or osteoarthritis.
AUTHOR: Mitsui H.; Tsuchiya N.; Okinaga S.; Matsuta K.; **Yoshimura K.**; Nishimura A.
CORPORATE SOURCE: A. Nishimura, Discovery Research Laboratories II, Pharmaceutical Discovery Res. Div., **Takeda**

Chemical Industries Ltd., 10 Wadai, Tsukuba 300-4247, Japan
SOURCE: Modern Rheumatology, (2001) 11/1 (34-39).
Refs: 30
ISSN: 1439-7595 CODEN: MROHA4
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
031 Arthritis and Rheumatism
033 Orthopedic Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB We investigated the expression of membrane-type matrix metalloproteinase (MT-**MMP**) and matrix metalloproteinase (**MMP**) mRNAs in synovial tissue from patients with rheumatoid arthritis (RA, n = 5) or osteoarthritis (OA, n = 5) by Northern blot analysis. Northern analysis demonstrated strong expression of MT1-**MMP**, MT3-**MMP**, **MMP**-1, and **MMP**-3 and weak expression of MT2-**MMP** and **MMP**-8 in synovial tissue from patients with RA or OA. MT4-**MMP** was not detected. No significant difference was shown in the expression of MT-**MMP** mRNAs between RA and OA. Synovial tissue of RA or OA patients expressed MT-**MMPs** as well as **MMPs**. These results indicate that, in addition to **MMPs**, MT1-**MMP**, MT3-**MMP**, and probably MT2-**MMP** may play a role in the degradation of bone and cartilage matrix in RA and OA. Such information may provide a clue to the development of a novel therapeutic approach targeted on the prevention of joint destruction.

L63 ANSWER 16 OF 20 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-372019 [35] WPIX
DOC. NO. NON-CPI: N2003-296671
DOC. NO. CPI: C2003-098842
TITLE: Screening promoters or inhibitors of proteoglycan decomposition as preventives for bone and joint diseases with use of cells expressing matrix metalloproteinase (**MMP**)-19 and membrane-type (MT)3-**MMP**, particularly for rheumatoid arthritis.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): HIKICHI, Y; **YOSHIMURA, K**
PATENT ASSIGNEE(S): (TAKE) **TAKEDA CHEM IND LTD**
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003029819	A1	20030410	(200335)*	JA	96
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
JP 2003189898	A	20030708	(200354)		38
AU 2002338108	A1	20030414	(200461)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE

WO 2003029819	A1	WO 2002-JP9949	20020926
JP 2003189898	A	JP 2002-280158	20020926
AU 2002338108	A1	AU 2002-338108	20020926

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002338108	A1 Based on	WO 2003029819

PRIORITY APPLN. INFO: JP 2001-303314 20010928
AN 2003-372019 [35] WPIX
AB WO2003029819 A UPAB: 20030603
NOVELTY - Screening compounds or their salts promoting or inhibiting proteoglycan decomposition is by using a combination of a protein based on the sequence of (I) of 508 amino acids, and another protein with an amino acid sequence identical or substantially similar to that of (II) of 457 amino acids, its partial peptide, is new. Both sequences given in the specification.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a similar method using DNA encoding the proteins with amino acids sequences of (I) and (II), or cells co-expressing the proteins or their partial peptide, optionally in the presence of animal-originated cartilage tissues or cells for co-culturing with a test compound, and measuring the proteoglycan decomposition activity with a control run for comparison;

(2) kits for screening compounds or their salts promoting or inhibiting proteoglycan decomposition containing the proteins or their partial peptides, or DNA encoding them, or cells expressing them;

(3) promoters or inhibitors of proteoglycan decomposition;

(4) drugs containing the thus screened promoters or inhibitors;

(5) preventives or remedies containing these screened compounds or their salts that inhibit or promote proteoglycan decomposition, or activity of the protein with an amino acid sequence of (I), its variant, their partial peptide or salts;

(6) preventing or treating bone and joint diseases by administering an effective dose of the compounds or their salts inhibiting or promoting activity of the protein with an amino acid sequence of (I) or its derivative; and

(7) the use of inhibitors or promoters of activity of the protein with an amino acid sequence of (I) or its derivative for producing preventives or remedies for bone and joint diseases.

ACTIVITY - Osteopathic.

No biological data is given.

MECHANISM OF ACTION - None given.

USE - The method is promoters or inhibitors of proteoglycan decomposition as preventives or remedies for bone and joint diseases, e.g. rheumatoid arthritis, osteoporosis and arthritis deformans (all claimed).

ADVANTAGE - With this method, the compounds regulating the decomposition activity of proteoglycan can be efficiently selected.

Dwg.0/0
ED 20030603

L63 ANSWER 17 OF 20 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-313193 [30] WPIX
DOC. NO. NON-CPI: N2003-249329
DOC. NO. CPI: C2003-082194
TITLE: Substances regulating the activity of proteins having increased expression in bone and joint disease for treatment and prevention of these diseases.
DERWENT CLASS: B04 D16 S03

INVENTOR(S): HIKICHI, Y; INAZUKA, M; **YOSHIMURA, K**
PATENT ASSIGNEE(S): (TAKE) **TAKEDA CHEM IND LTD**
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003022300	A1	20030320	(200330)*	JA	154
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JP 2003183177	A	20030703	(200352)		66
EP 1426056	A1	20040609	(200438)	EN	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR					
AU 2002335369	A1	20030324	(200461)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003022300	A1	WO 2002-JP9140	20020909
JP 2003183177	A	JP 2002-262564	20020909
EP 1426056	A1	EP 2002-798045	20020909
		WO 2002-JP9140	20020909
AU 2002335369	A1	AU 2002-335369	20020909

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1426056	A1 Based on	WO 2003022300
AU 2002335369	A1 Based on	WO 2003022300

PRIORITY APPLN. INFO: JP 2001-303390 20010928; JP
2001-273914 20010910; JP
2001-281472 20010917; JP
2001-300289 20010928; JP
2001-300347 20010928; JP
2001-300417 20010928

AN 2003-313193 [30] WPIX
AB WO2003022300 A UPAB: 20030513
NOVELTY - Agents for the treating and preventing bone and joint diseases which regulate the activity or expression of human proteins (I) showing increased expression in diseased bone and joint tissue e.g. DIO2 (type 2 iodothyronine deiodinase); ANKH (pyrophosphate transporter); SHOX2 (short stature homeobox 2); TASK4 (potassium ion channel protein); EphA3 (Eph receptor A3); and/or **MMP16** (matrix metalloproteinase 16), are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for

(1) agents for prevention and treatment of bone and joint diseases, containing DNA complementary to all or part of DNA encoding proteins (I), or containing antibodies to proteins (I);

(2) diagnostic reagents for bone and joint diseases, containing DNA complementary to all or part of DNA encoding proteins (I), or containing antibodies to proteins (I);

(3) screening agents for the treatment and prevention of bone and joint diseases, in which the effect of the test substance on the activity or expression of proteins (I) is determined;

(4) kits for the screening method;

(5) agents for the treatment and prevention of bone and joint diseases, identified by the method;

(6) treatment and prevention of bone and joint diseases, using the agents of (5).

ACTIVITY - Antiarthritic; Antirheumatic; Osteopathic; Antiinflammatory.

MECHANISM OF ACTION - Iodothyronine deiodinase inhibitor; Pyrophosphate transport inhibitor; Short stature homeobox 2 inhibitor; Potassium ion transport inhibitor; Eph receptor antagonist; Matrix metalloproteinase 16 inhibitor.

USE - Prevention, treatment and diagnosis of diseases involving abnormal formation or development of bone and cartilage (such as arthritis deformans), chronic rheumatoid arthritis, synovial inflammation, or localized arthritis (such as 'tennis elbow').

Dwg.0/4

ED 20030513

L63 ANSWER 18 OF 20 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-227106 [28] WPIX
DOC. NO. NON-CPI: N2002-174317
DOC. NO. CPI: C2002-069140
TITLE: Transgenic mammal containing foreign **MMP**-19 gene for use as a model for bone and cartilage diseases.
DERWENT CLASS: B04 D16 P14 S03
INVENTOR(S): HOSONO, K; NISHIDA, M; NISHIMURA, A; **YOSHIMURA, K**
PATENT ASSIGNEE(S): (TAKE) **TAKEDA CHEM IND LTD**
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002011530	A1	20020214	(200228)*	JA	47
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W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001077716	A	20020218	(200244)		
JP 2002360117	A	20021217	(200312)		18

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002011530	A1	WO 2001-JP6826	20010808
AU 2001077716	A	AU 2001-77716	20010808
JP 2002360117	A	JP 2001-240948	20010808

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001077716	A	Based on	WO 2002011530

PRIORITY APPLN. INFO: JP 2000-241748 20000809

AN 2002-227106 [28] WPIX
AB WO 200211530 A UPAB: 20020502
NOVELTY - Non-human transgenic mammal containing recombinant DNA encoding a foreign **MMP**-19 gene or its modified form is new.
DETAILED DESCRIPTION - Non-human transgenic mammal transformed with recombinant DNA encoding a foreign **MMP**-19 gene or its modified form is new,. INDEPENDENT CLAIMS are also included for:
(1) cover expression vectors for **MMP**-19 gene in non-human mammals;
(2) cells transformed by the vectors;
(3) a method for screening compounds for use in the prevention and treatment of extracellular matrix disorders, using the transgenic mammals;
(4) compounds identified by the screening method;
(5) a method for treatment of extracellular matrix disorders using the identified compounds;
(6) fertilized ova transformed by the foreign **MMP**-19 gene; and
(7) the production of transgenic mammals by implantation of the ova and bringing to term.
ACTIVITY - Osteopathic; Antiarthritic; Antirheumatic; Ophthalmological; Cytostatic.
MECHANISM OF ACTION - None given.
USE - Identification of agents for the treatment and prevention of extracellular matrix disorders including chondrogenic failure, osteogenetic failure, osteoporosis, arthritis deformans, rheumatoid arthritis, synovitis, metabolic arthritis, eye disease, malignant tumors, and associated complications. The transgenic mammals are a model for joint and bone diseases including deformation and shortening of limbs, cranial deformation, defective bite, tooth elongation, and defects of lumbar and tail vertebrae.
Dwg.0/3
ED 20020502

L63 ANSWER 19 OF 20 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-271056 [23] WPIX
DOC. NO. CPI: C2000-082646
TITLE: Novel protein belong to A disintegrin and **metalloprotease** family, with protease activity and extracellular matrix digesting enzyme activity, for gene diagnosis and developing drugs for treating e.g. sciatica and glomerulitis.
DERWENT CLASS: B04 D16
INVENTOR(S): HIKICHI, Y; NISHIMURA, A; **YOSHIMURA, K**
PATENT ASSIGNEE(S): (TAKE) **TAKEDA CHEM IND LTD**; (HIKI-I) HIKICHI Y; (NISH-I) NISHIMURA A; (YOSH-I) YOSHIMURA K
COUNTRY COUNT: 88
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000014227	A1	20000316	(200023)*	JA	108
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AU 9954479	A	20000327	(200032)		
JP 2000139480	A	20000523	(200033)		48
EP 1111047	A2	20010627	(200137)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT					

	RO	SE	SI	
JP 2000568971	X		20011120	(200203)
US 6680189	B1		20040120	(200407)
US 2004132157	A1		20040708	(200445)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000014227	A1	WO 1999-JP4766	19990902
AU 9954479	A	AU 1999-54479	19990902
JP 2000139480	A	JP 1999-248436	19990902
EP 1111047	A2	EP 1999-940629	19990902
		WO 1999-JP4766	19990902
JP 2000568971	X	WO 1999-JP4766	19990902
		JP 2000-568971	19990902
US 6680189	B1	WO 1999-JP4766	19990902
		US 2001-786256	20010510
US 2004132157	A1 Div ex	WO 1999-JP4766	19990902
	Div ex	US 2001-786256	20010510
		US 2003-726148	20031202

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9954479	A Based on	WO 2000014227
EP 1111047	A2 Based on	WO 2000014227
JP 2000568971	X Based on	WO 2000014227
US 6680189	B1 Based on	WO 2000014227
US 2004132157	A1 Div ex	US 6680189

PRIORITY APPLN. INFO: JP 1998-250115 19980903

AN 2000-271056 [23] WPIX

AB WO 200014227 A UPAB: 20000516

NOVELTY - Protein (I) comprising a sequence of 96 amino acids (aa), given in the specification, or its salt, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(i) a peptide fragment of (I) or its salt which comprising a sequence of 10 aa (II), given in the specification;

(ii) a DNA encoding (I);

(iii) a DNA (III) comprising a sequence of 288 base pairs (bp), given in the specification, encoding a fragment of (I);

(iv) a recombinant vector containing a DNA encoding (I);

(v) a transformant obtained with the recombinant vector of (iv);

(vi) producing (I) or its salt by culturing the transformant of (v);

(vii) an antibody with specificity to (I), its peptide fragments or salts;

(viii) a diagnostic reagent comprising the DNA encoding (I) or antibody of (vii);

(ix) an agent comprising (I), its fragments or salts;

(x) a drug comprising (I), its fragments or salts, which can be used to prevent or treat intervertebral hernia, sciatica, glomerulitis, diabetic nephropathy, hepatic fibrosis, pulmonary fibrosis or osteopetrosis;

(xi) screening for compounds or salts that can promote or inhibit the protease activity by using the protein or its salt;

(xii) a kit for screening for compounds or salts capable of promoting or inhibiting the protease activity containing the protein or its salt;

(xiii) protease promoters or inhibitors identified by the screen of (xi);

(xiv) drugs containing the protease promoters or inhibitors of (xiii);

(xv) an extracellular matrix digesting agent comprising a protein with 201 aa sequence ((IV); given in the specification), where the extracellular matrix is a proteoglycan, and can be used to prevent or treat intervertebral hernia, sciatica, glomerulitis, diabetic nephropathy, hepatic fibrosis, pulmonary fibrosis or osteopetrosis;

(xvi) a drug composition containing the agent of (xv);

(xvii) screening for compounds or salts capable of promoting or inhibiting the extracellular matrix digesting enzyme activity using (IV);

(xviii) kits comprising (I) or its salt, for screening for compounds or salts that can promote or inhibit the extracellular matrix digesting enzyme activity;

(xix) promoters or inhibitors of the extracellular matrix digesting enzyme activity obtained using the kits of (xviii);

(xx) drugs containing the promoters or inhibitors of the extracellular matrix digesting enzyme activity;

(xxi) a diagnostic reagent comprising (I) or its salt;

(xxii) detecting a proteoglycan digesting enzyme gene by culturing a recombinant host containing the gene, and animal-derived cartilage or cartilage matrix-producing cells, and determining the amount of glycosaminoglycan sulfate in the culture supernatant solution;

(xxiii) screening for inhibitors or promoters of the proteoglycan digesting enzyme comprising:

(a) introducing a protein with proteoglycan digesting enzyme activity, preferably comprising (I) and/or (IV), to a transformant, or particularly an animal cell;

(b) obtaining animal-derived cartilage or cartilage matrix-producing cells and mix-culturing with a sample; and

(c) determining the glycosaminoglycan sulfate in the culture supernatant solution; and

(xxiv) a non-human animal containing (and expressing) a DNA encoding (I), or its variants.

Glu Cys Thr Asn Ile Cys Cys Asp Ala Lys (II)

USE - The protein, peptide fragment and antibody are useful for gene diagnosis and in the development of drugs to prevent or treat intervertebral hernia, sciatica, glomerulitis, diabetic nephropathy, hepatic fibrosis, pulmonary fibrosis or osteopetrosis (claimed).

ADVANTAGE - The protein belongs to the ADAM family.

Dwg.0/5

ED 20000516

L63 ANSWER 20 OF 20 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 1997-535841 [49] WPIX
DOC. NO. CPI: C1997-171397
TITLE: New matrix **metalloprotease** from human or rat - useful for treatment, prevention and diagnosis of e.g. diabetic nephropathy, glomerulonephritis, fibrosis, liver cirrhosis etc..
DERWENT CLASS: B04 D16
INVENTOR(S): HIKICHI, Y; NISHIMURA, A; **YOSHIMURA, K**; ATSUSHI, N; KOJI, Y; YUICHI, H
PATENT ASSIGNEE(S): (TAKE) **TAKEDA CHEM IND LTD**
COUNTRY COUNT: 76
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG

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       LK LR LT LV MD MG MK MN MX NO NZ PL RO RU SG SI SK TJ TM TR TT UA
       US UZ VN YU
AU 9724064      A  19971112 (199811)
JP 10080283     A  19980331 (199823)       42
EP 897426       A1 19990224 (199912)  EN
    R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 6566116      B1 20030520 (200336)
US 2003099631   A1 20030529 (200337)
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APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9740157	A1	WO 1997-JP1433	19970424
AU 9724064	A	AU 1997-24064	19970424
JP 10080283	A	JP 1997-106511	19970424
EP 897426	A1	EP 1997-919679	19970424
		WO 1997-JP1433	19970424
US 6566116	B1	WO 1997-JP1433	19970424
		US 1999-171545	19990726
US 2003099631	A1 Div ex	WO 1997-JP1433	19970424
	Div ex	US 1999-171545	19990726
		US 2002-251482	20020919

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9724064	A Based on	WO 9740157
EP 897426	A1 Based on	WO 9740157
US 6566116	B1 Based on	WO 9740157

PRIORITY APPLN. INFO: JP 1996-104902 19960425

AN 1997-535841 [49] WPIX

AB WO 9740157 A UPAB: 19971211

A protein (A), with the 508 amino acid (aa) sequence given in the specification, its salts, and its equivalents, are new. Also new are: (1) an active fragment (Aa) of (A); (2) a DNA (I) encoding (A) (sequences of 1524 bp (human) and 1551 bp (rat) given in the specification); (3) a recombinant vector containing (I); (4) a cell transformed with the vector of (3); (5) an antibody (Ab) against (A) and (Aa); (6) a method (and kit) for screening to identify compounds (B) that activate or inhibit (A) and (Aa); and (7) (B) identified by the method of (6).

USE - (A), is a matrix **metalloprotease.** (A), (Aa) and (B) that activate (A) are useful for treating or preventing conditions in which endogenous (A) activity is suppressed, specifically diabetic nephropathy, glomerulonephritis, pulmonary fibrosis, hepatolineal fibrosis, hepatocirrhosis, osteopetrosis and herniated discs. (A) and (Aa) are also used in the screening method of (6). (I) are used to produce recombinant (A) and (Aa), also for gene therapy of the specified conditions (all claimed). Fragments of (I) can be used to detect genetic abnormalities. Ab are used for quantitative immunoassay of (A) or (Aa), particularly for diagnosis, also for histological staining and for purification of (A). (B) which are inhibitors (including antisense nucleic acid) are useful for treating or preventing a wide range of conditions where (A) levels are elevated, e.g. wounds, rheumatoid arthritis,

osteoarthritis, cancer (including metastases), corneal or gastric ulcers, atherosclerosis, multiple sclerosis, cachexia, lymphoma, diabetes, asthma (and other allergies), acute pancreatitis, myocardial infarction, graft vs. host disease etc. Also, transgenic animals that overexpress (A) can be used to screen for (B), as a source of cells for studying the function of (A) and for the production of (A).

Dwg.0/6

ED 19971211

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=>

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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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STRUCTURE FILE UPDATES:   25 NOV 2004  HIGHEST RN 788788-78-3
DICTIONARY FILE UPDATES:  25 NOV 2004  HIGHEST RN 788788-78-3

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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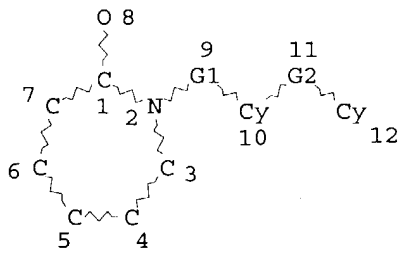


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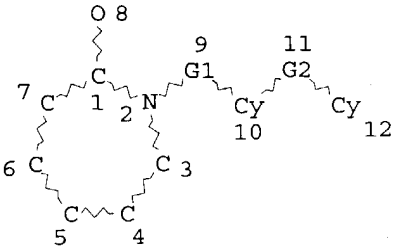

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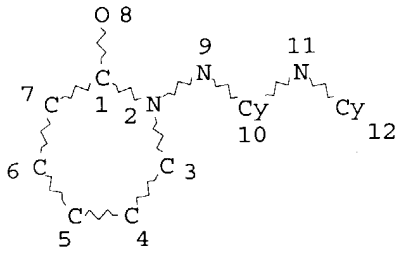

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DEFAULT MLEVEL IS ATOM
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STEREO ATTRIBUTES: NONE
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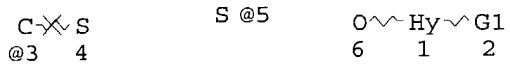

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L2               STR
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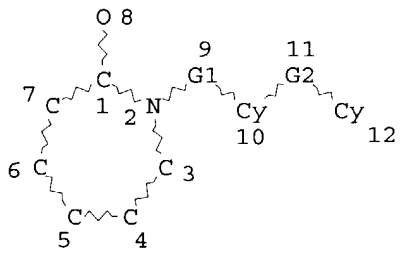
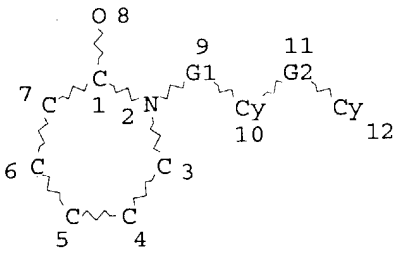



```
REP G1=(0-6) 13
REP G2=(0-6) 14
NODE ATTRIBUTES:
NSPEC   IS RC     AT  13
NSPEC   IS RC     AT  14
CONNECT IS E1  RC AT   8
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
```

NUMBER OF NODES IS 14

STEREO ATTRIBUTES: NONE
L3 3855 SEA FILE=REGISTRY SUB=L1 SSS FUL L2
L16 STR

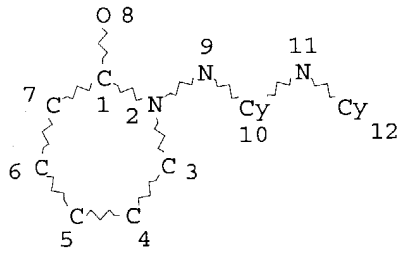


C @13 C @14

REP G1=(0-4) 13
REP G2=(0-4) 14
NODE ATTRIBUTES:
NSPEC IS RC AT 13
NSPEC IS RC AT 14
CONNECT IS E1 RC AT 8
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 14

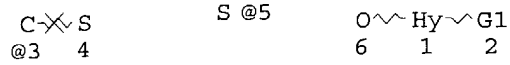
STEREO ATTRIBUTES: NONE
L18 STR



NODE ATTRIBUTES:
NSPEC IS RC AT 9
NSPEC IS RC AT 11
CONNECT IS E1 RC AT 8
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 12

STEREO ATTRIBUTES: NONE
L21 3042 SEA FILE=REGISTRY SUB=L3 SSS FUL (L16 OR L18)
L26 119 SEA FILE=REGISTRY ABB=ON PLU=ON L21 AND ?THIO?/CNS
L30 STR



```
VAR G1=3/5
NODE ATTRIBUTES:
NSPEC   IS RC     AT   3
NSPEC   IS RC     AT   4
NSPEC   IS RC     AT   5
CONNECT IS E1  RC AT   6
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS M6 C  M1 N  AT   1

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS   6

STEREO ATTRIBUTES: NONE
L32          104 SEA FILE=REGISTRY SUB=L21 SSS FUL L30
L42           22 SEA FILE=REGISTRY ABB=ON  PLU=ON  L26 NOT L32
L43            2 SEA FILE=REGISTRY ABB=ON  PLU=ON  L42 AND ?SPIRO?/CNS


=> fil reg

FILE 'REGISTRY' ENTERED AT 11:35:21 ON 27 NOV 2004
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STRUCTURE FILE UPDATES:   25 NOV 2004  HIGHEST RN 788788-78-3
DICTIONARY FILE UPDATES:  25 NOV 2004  HIGHEST RN 788788-78-3

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> analyze l43
ENTER ANSWER NUMBER OR RANGE (1-):1-
ENTER DISPLAY CODE (CHEM) OR ?:lc
L45          ANALYZE L43 1- LC :        5 TERMS

=> d
L45          ANALYZE L43 1- LC :        5 TERMS

TERM #    # OCC   # DOC   % DOC LC
------ -------- ------ ------ ---------------
     1        2      2 100.00 CA
     2        2      2 100.00 CAPLUS
     3        1      1  50.00 TOXCENTER
     4        1      1  50.00 USPATFULL
```

```
     5        1        1  50.00 USPAT2
*********  END OF L45***


=> file stnguide

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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Nov 19, 2004 (20041119/UP).

=> => fil hcap

FILE 'HCAPLUS' ENTERED AT 11:38:52 ON 27 NOV 2004
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FILE COVERS 1907 - 27 Nov 2004  VOL 141 ISS 23
FILE LAST UPDATED: 26 Nov 2004  (20041126/ED)

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 substance identification.


=> fil uspatfull

FILE 'USPATFULL' ENTERED AT 11:38:56 ON 27 NOV 2004
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 25 Nov 2004 (20041125/PD)
FILE LAST UPDATED: 25 Nov 2004 (20041125/ED)
HIGHEST GRANTED PATENT NUMBER: US6823528
HIGHEST APPLICATION PUBLICATION NUMBER: US2004237163
CA INDEXING IS CURRENT THROUGH 25 Nov 2004 (20041125/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 25 Nov 2004 (20041125/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2004

>>>  USPAT2 is now available.  USPATFULL contains full text of the     <<<
>>>  original, i.e., the earliest published granted patents or         <<<
>>>  applications.  USPAT2 contains full text of the latest US         <<<
>>>  publications, starting in 2001, for the inventions covered in     <<<
>>>  USPATFULL.  A USPATFULL record contains not only the original     <<<
>>>  published document but also a list of any subsequent              <<<
>>>  publications.  The publication number, patent kind code, and      <<<
```

```
>>>  publication date for all the US publications for an invention     <<<
>>>  are displayed in the PI (Patent Information) field of USPATFULL  <<<
>>>  records and may be searched in standard search fields, e.g., /PN, <<<
>>>  /PK, etc.                                                         <<<

>>>  USPATFULL and USPAT2 can be accessed and searched together        <<<
>>>  through the new cluster USPATALL.  Type FILE USPATALL to          <<<
>>>  enter this cluster.                                               <<<
>>>                                                                    <<<
>>>  Use USPATALL when searching terms such as patent assignees,       <<<
>>>  classifications, or claims, that may potentially change from     <<<
>>>  the earliest to the latest publication.                           <<<

This file contains CAS Registry Numbers for easy and accurate
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=> fil toxcenter

FILE 'TOXCENTER' ENTERED AT 11:38:59 ON 27 NOV 2004
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FILE COVERS 1907 TO 23 Nov 2004 (20041123/ED)

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identification.

TOXCENTER has been enhanced with new files segments and search fields.
See HELP CONTENT for more information.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the
MeSH 2004 vocabulary.  See http://www.nlm.nih.gov/mesh/ and
http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
description of changes.

=> file stnguide

FILE 'STNGUIDE' ENTERED AT 11:39:03 ON 27 NOV 2004
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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Nov 19, 2004 (20041119/UP).

=> => d que l49
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L2              STR
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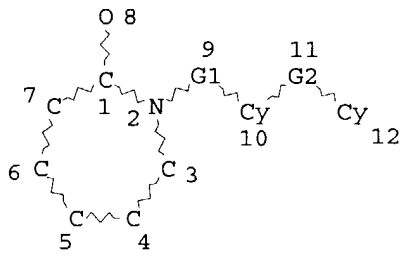
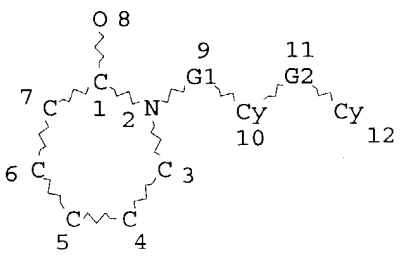



```
REP G1=(0-6) 13
```

REP G2=(0-6) 14
NODE ATTRIBUTES:
NSPEC IS RC AT 13
NSPEC IS RC AT 14
CONNECT IS E1 RC AT 8
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 14

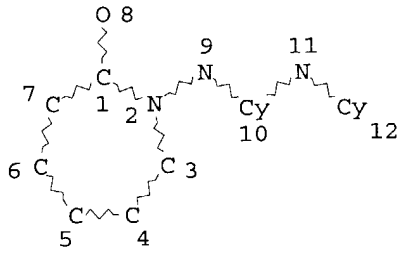
STEREO ATTRIBUTES: NONE
L3 3855 SEA FILE=REGISTRY SUB=L1 SSS FUL L2
L16 STR



REP G1=(0-4) 13
REP G2=(0-4) 14
NODE ATTRIBUTES:
NSPEC IS RC AT 13
NSPEC IS RC AT 14
CONNECT IS E1 RC AT 8
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 14

STEREO ATTRIBUTES: NONE
L18 STR



NODE ATTRIBUTES:
NSPEC IS RC AT 9
NSPEC IS RC AT 11
CONNECT IS E1 RC AT 8
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

```
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  12

STEREO ATTRIBUTES: NONE
L21         3042 SEA FILE=REGISTRY SUB=L3 SSS FUL (L16 OR L18)
L26          119 SEA FILE=REGISTRY ABB=ON  PLU=ON  L21 AND ?THIO?/CNS
L30              STR
```


```
VAR G1=3/5
NODE ATTRIBUTES:
NSPEC   IS RC     AT   3
NSPEC   IS RC     AT   4
NSPEC   IS RC     AT   5
CONNECT IS E1  RC AT   6
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS M6 C  M1 N  AT   1

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS   6

STEREO ATTRIBUTES: NONE
L32          104 SEA FILE=REGISTRY SUB=L21 SSS FUL L30
L34           13 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L32
L42           22 SEA FILE=REGISTRY ABB=ON  PLU=ON  L26 NOT L32
L43            2 SEA FILE=REGISTRY ABB=ON  PLU=ON  L42 AND ?SPIRO?/CNS
L46            3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L43
L49           16 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L34 OR L46


=> d que nos l50
L1  (    156603)SEA FILE=REGISTRY ABB=ON  PLU=ON  NC6/ESS
L2              STR
L3           3855 SEA FILE=REGISTRY SUB=L1 SSS FUL L2
L16             STR
L18             STR
L21          3042 SEA FILE=REGISTRY SUB=L3 SSS FUL (L16 OR L18)
L26           119 SEA FILE=REGISTRY ABB=ON  PLU=ON  L21 AND ?THIO?/CNS
L30             STR
L32           104 SEA FILE=REGISTRY SUB=L21 SSS FUL L30
L36             9 SEA FILE=USPATFULL ABB=ON  PLU=ON  L32
L42            22 SEA FILE=REGISTRY ABB=ON  PLU=ON  L26 NOT L32
L43             2 SEA FILE=REGISTRY ABB=ON  PLU=ON  L42 AND ?SPIRO?/CNS
L47             4 SEA FILE=USPATFULL ABB=ON  PLU=ON  L43
L50            13 SEA FILE=USPATFULL ABB=ON  PLU=ON  L47 OR L36


=> d que nos l51
L1  (    156603)SEA FILE=REGISTRY ABB=ON  PLU=ON  NC6/ESS
L2              STR
L3           3855 SEA FILE=REGISTRY SUB=L1 SSS FUL L2
L16             STR
L18             STR
L21          3042 SEA FILE=REGISTRY SUB=L3 SSS FUL (L16 OR L18)
L26           119 SEA FILE=REGISTRY ABB=ON  PLU=ON  L21 AND ?THIO?/CNS
L30             STR
```

```
L32          104 SEA FILE=REGISTRY SUB=L21 SSS FUL L30
L37            1 SEA FILE=TOXCENTER ABB=ON  PLU=ON  L32
L42           22 SEA FILE=REGISTRY ABB=ON  PLU=ON  L26 NOT L32
L43            2 SEA FILE=REGISTRY ABB=ON  PLU=ON  L42 AND ?SPIRO?/CNS
L48            2 SEA FILE=TOXCENTER ABB=ON  PLU=ON  L43
L51            3 SEA FILE=TOXCENTER ABB=ON  PLU=ON  L37 OR L48


=> dup rem l49 l50 l51

FILE 'HCAPLUS' ENTERED AT 11:43:54 ON 27 NOV 2004
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PROCESSING COMPLETED FOR L49
PROCESSING COMPLETED FOR L50
PROCESSING COMPLETED FOR L51
L52           27 DUP REM L49 L50 L51 (5 DUPLICATES REMOVED)
                 ANSWERS '1-16' FROM FILE HCAPLUS
                 ANSWERS '17-27' FROM FILE USPATFULL

=> d iall hitstr

L52  ANSWER 1 OF 27  HCAPLUS  COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER:         2003:491200  HCAPLUS
DOCUMENT NUMBER:          139:53022
ENTRY DATE:               Entered STN:  27 Jun 2003
TITLE:                    Preparation of thiadiazoline derivatives as antitumor
                          agents
INVENTOR(S):              Murakata, Chikara; Kato, Kazuhiko; Ohta, Yoshihisa;
                          Nakai, Ryuichiro; Yamashita, Yoshinori; Takahashi,
                          Takeshi; Nakano, Tomohisa; Ino, Yoji
PATENT ASSIGNEE(S):       Kyowa Hakko Kogyo Co., Ltd., Japan; Fuji Photo Film
                          Co., Ltd.
SOURCE:                   PCT Int. Appl., 154 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 Japanese
INT. PATENT CLASSIF.:
            MAIN:         C07D285-135
       SECONDARY:         C07D417-04; C07D285-14; A61K031-433; A61K031-4439;
                          A61K031-497; A61K031-5377; A61P035-00
CLASSIFICATION:           28-10 (Heterocyclic Compounds (More Than One Hetero
                          Atom))
                          Section cross-reference(s): 1, 63
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2003051854         A1    20030626    WO 2002-JP12961         20021211
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
```

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ,
CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1454903	A1	20040908	EP 2002-788786	20021211

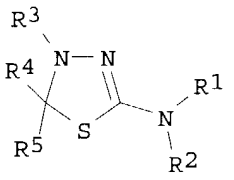
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK

PRIORITY APPLN. INFO.:	JP 2001-377456	A 20011211
	JP 2002-237399	A 20020816
	WO 2002-JP12961	W 20021211

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003051854	ICM	C07D285-135
	ICS	C07D417-04; C07D285-14; A61K031-433; A61K031-4439; A61K031-497; A61K031-5377; A61P035-00
EP 1454903	ECLA	A61K031/433; A61K031/4439; A61K031/497; A61K031/5377; C07D285/12D6D3

OTHER SOURCE(S): MARPAT 139:53022
GRAPHIC IMAGE:



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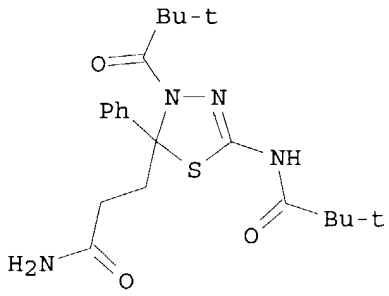

II

ABSTRACT:
The title thiadiazoline derivs. with general formula of I [wherein R1 and R4 = independently H, (un)substituted alkyl, alkynyl, alkenyl, cycloalkyl, heterocyclyl, or aryl; R2 = H, (un)substituted alkyl, alkynyl, alkenyl, cycloalkyl, COR6, or CSR6; R6 = H, (un)substituted alkyl, alkenyl, cycloalkyl, aryl, heterocyclyl, amino, OH, SH, or SO2R7; R7 = (un)substituted alkyl, alkenyl, aryl, or heterocyclyl; or R1 and R2 together form an (un)substituted heterocycle with the nitrogen atom attached; R5 = (un)substituted alkyl, alkynyl, alkenyl, cycloalkyl, heterocyclyl, or aryl; or R4 and R5 together form an (un)substituted ring with the carbon atom attached; R3 = H, COR6, or CSR6] and pharmaceutically acceptable salts thereof are prepared as antitumor agents. For example, the compound II was prepared in a multi-step synthesis in moderate yield. II showed inhibitory activity with GI50 of 0.061 μM against human large bowel cancer cell growth. Formulations containing I as an active ingredient were also described.

SUPPL. TERM: phenyl amino thiadiazoline antitumor agent prepn human formulation

INDEX TERM: Antitumor agents
Human
Neoplasm
(preparation of thiadiazoline derivs. as antitumor agents)

INDEX TERM: 72926-06-8P 72926-24-0P 332389-23-8P 433235-71-3P
510764-26-8P 546110-44-5P 546110-53-6P 546110-55-8P
546110-57-0P 546110-78-5P 546110-87-6P 546110-90-1P
546111-01-7P 546111-04-0P 546111-07-3P 546111-11-9P
546111-20-0P 546111-21-1P 546111-23-3P 546111-26-6P
546111-27-7P 546111-35-7P 546111-36-8P 546111-39-1P
546111-40-4P 546111-41-5P 546111-42-6P 546111-43-7P
546111-44-8P 546111-46-0P 546111-49-3P 546111-64-2P
546111-67-5P 546111-69-7P 546111-70-0P 546111-72-2P
546111-74-4P 546111-76-6P 546111-78-8P 546111-79-9P
546111-87-9P 546111-91-5P 546111-92-6P 546111-99-3P
546112-01-0P 546112-06-5P 546112-07-6P 546112-11-2P
546112-12-3P 546112-13-4P 546112-14-5P 546112-16-7P
546112-18-9P 546112-19-0P
ROLE: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(antitumor agent; preparation of thiadiazoline derivs. as antitumor agents)

INDEX TERM: 72926-23-9P 89992-30-3P 107261-68-7P 150007-07-1P
150007-08-2P 150007-09-3P 332389-24-9P 333776-50-4P
356773-12-1P 356773-13-2P 403518-07-0P 403518-08-1P
443105-46-2P 443105-56-4P 443105-64-4P 443105-73-5P
443105-83-7P 510717-71-2P 546110-41-2P 546110-42-3P
546110-43-4P 546110-45-6P 546110-46-7P 546110-47-8P
546110-48-9P 546110-49-0P 546110-50-3P 546110-51-4P
546110-52-5P 546110-54-7P 546110-56-9P 546110-58-1P
546110-59-2P 546110-60-5P 546110-61-6P 546110-62-7P
546110-63-8P 546110-64-9P 546110-65-0P 546110-66-1P
546110-67-2P 546110-68-3P 546110-69-4P 546110-70-7P
546110-71-8P 546110-72-9P 546110-73-0P 546110-74-1P
546110-75-2P 546110-76-3P 546110-77-4P 546110-80-9P
546110-82-1P 546110-85-4P 546110-86-5P 546110-88-7P
546110-89-8P 546110-91-2P 546110-92-3P 546110-93-4P
546110-94-5P 546110-95-6P 546110-96-7P 546110-97-8P
546110-98-9P 546110-99-0P 546111-00-6P 546111-02-8P
546111-03-9P 546111-05-1P 546111-06-2P 546111-08-4P
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546111-14-2P 546111-15-3P 546111-16-4P 546111-17-5P
546111-18-6P 546111-19-7P 546111-22-2P 546111-24-4P
546111-25-5P 546111-28-8P 546111-29-9P 546111-30-2P
546111-31-3P 546111-32-4P 546111-33-5P 546111-34-6P
546111-37-9P 546111-38-0P 546111-45-9P 546111-47-1P
546111-48-2P 546111-50-6P 546111-51-7P 546111-52-8P
546111-53-9P 546111-54-0P 546111-55-1P 546111-56-2P
546111-57-3P 546111-58-4P 546111-59-5P 546111-60-8P
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546111-66-4P 546111-68-6P 546111-71-1P 546111-73-3P
546111-75-5P **546111-77-7P** 546111-80-2P
546111-81-3P 546111-82-4P 546111-83-5P 546111-84-6P
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546111-96-0P 546111-97-1P 546111-98-2P 546112-00-9P
546112-02-1P 546112-03-2P 546112-04-3P 546112-05-4P
546112-08-7P 546112-09-8P 546112-10-1P 546112-15-6P
546112-17-8P 546112-20-3P
ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(antitumor agent; preparation of thiadiazoline derivs. as antitumor agents)

INDEX TERM: 777-16-2P 1752-30-3P 2302-93-4P 3115-21-7P
3689-17-6P 3766-55-0P 5351-71-3P 5351-77-9P
5351-80-4P 5424-45-3P 6699-22-5P 6839-90-3P
7410-54-0P 7420-37-3P 7441-53-4P 7651-47-0P
13370-86-0P 13466-30-3P 14923-71-8P 16546-08-0P
22233-81-4P 22397-20-2P 27421-65-4P 40104-24-3P
41904-33-0P 54688-10-7P 56062-81-8P 65110-11-4P
74227-66-0P 78597-06-5P 91994-49-9P 106010-23-5P
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387847-12-3P 499142-35-7P 546112-21-4P 546112-22-5P
546112-23-6P 546112-24-7P 546112-25-8P 546112-26-9P
546112-27-0P 546112-28-1P 546112-29-2P 546112-30-5P
546112-31-6P 546112-32-7P 546112-33-8P 546112-34-9P
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546112-43-0P 546112-44-1P 546112-45-2P 546112-46-3P
546112-47-4P 546112-48-5P 546112-49-6P 546112-50-9P
546112-78-1P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of thiadiazoline derivs. as antitumor agents)

INDEX TERM: 57-06-7, Allyl isothiocyanate 67-64-1, Acetone, reactions
79-19-6, Thiosemicarbazide 79-30-1, Isobutyryl chloride
79-44-7, Dimethylcarbamoyl chloride 83-33-0, 1-Indanone
88-15-3, 2-Acetylthiophene 89-74-7, 2',4'-Dimethylacetophenone 93-08-3, 2'-Acetonaphthone 93-55-0, Propiophenone 97-72-3, Isobutyric acid anhydride
98-86-2, Acetophenone, reactions 99-02-5,
3'-Chloroacetophenone 99-91-2, 4'-Chloroacetophenone
99-93-4, 4'-Hydroxyacetophenone 100-06-1,
4'-Methoxyacetophenone 100-19-6, 4'-Nitroacetophenone
100-39-0, Benzyl bromide 100-83-4, 3-Hydroxybenzaldehyde
106-31-0, Butyric acid anhydride 107-08-4, Propyl iodide
108-91-8, Cyclohexylamine, reactions 108-94-1,
Cyclohexanone, reactions 109-73-9, Butylamine, reactions
109-83-1, 2-(Methylamino)ethanol 110-89-4, Piperidine,
reactions 110-91-8, Morpholine, reactions 111-42-2,
Diethanolamine, reactions 118-93-4, 2'-Hydroxyacetophenone
119-61-9, Benzophenone, reactions 121-71-1,
3'-Hydroxyacetophenone 121-89-1, 3'-Nitroacetophenone
122-00-9, 4'-Methylacetophenone 122-57-6,
Benzylideneacetone 123-62-6, Propionic acid anhydride
142-61-0, Hexanoyl chloride 349-76-8, 3'-(Trifluoromethyl)acetophenone 350-03-8, 3-Acetylpyridine
403-42-9, 4'-Fluoroacetophenone 445-27-2,
2'-Fluoroacetophenone 455-36-7, 3'-Fluoroacetophenone
497-38-1, 2-Norbornanone 502-56-7, 5-Nonanone 529-34-0,
α-Tetralone 530-93-8, β-Tetralone 577-16-2,
2'-Methylacetophenone 577-56-0, 2-Acetylbenzoic acid
577-59-3, 2'-Nitroacetophenone 579-74-8,
2'-Methoxyacetophenone 585-74-0, 3'-Methylacetophenone
586-37-8, 3'-Methoxyacetophenone 591-78-6, 2-Hexanone
611-70-1, Isopropyl phenyl ketone 616-30-8,
3-Amino-1,2-propanediol 626-58-4, 4-Methylpiperidine

927-58-2, 4-Bromobutyryl chloride 936-59-4, 3-Chloropropiophenone 941-98-0, 1'-Acetonaphthone 1009-14-9, Butyl phenyl ketone 1072-83-9, 2-Acetylpyrrole 1122-54-9, 4-Acetylpyridine 1122-62-9, 2-Acetylpyridine 1192-62-7, 2-Acetylfuran 1197-09-7, 3',4'-Dihydroxyacetophenone 1443-80-7, 4-Acetylbenzonitrile 1468-39-9, Isovaleric acid anhydride 1468-83-3, 3-Acetylthiophene 1501-04-8, 4-(Carbomethoxy)butyrophenone 1501-26-4 1579-15-3, 2-Acetoxy-1-indanone 2040-04-2, 2',6'-Dimethoxyacetophenone 2142-68-9, 2'-Chloroacetophenone 2142-69-0, 2'-Bromoacetophenone 2550-26-7, Benzylacetone 3282-30-2, Pivaloyl chloride 3481-02-5, Cyclopropyl phenyl ketone 3506-36-3, 3-(Dimethylamino)propiophenone 4224-70-8, 6-Bromohexanoic acid 4346-94-5, Thiosemicarbazide monohydrochloride 4509-90-4, 5-Bromovaleryl chloride 4524-93-0, Cyclopentylcarbonyl chloride 5370-25-2, 1-(5-Bromo-2-thienyl)ethanone 5468-37-1, 2-Aminoacetophenone hydrochloride 6136-68-1, 3-Acetylbenzonitrile 6610-29-3, 4-Methylthiosemicarbazide 10487-71-5, Crotonoyl chloride 13431-34-0, 4-Ethylthiosemicarbazide 13679-72-6, 2-Acetyl-3-methylthiophene 16819-79-7 22047-25-2, Acetylpyrazine 22720-75-8, 2-Acetylbenzothiophene 24295-03-2, 2-Acetylthiazole 24424-99-5, Di-tert-butyl dicarbonate 25333-24-8 26976-88-5 38870-89-2, Methoxyacetyl chloride 40635-66-3, 2-Acetoxyisobutyryl chloride 42877-08-7, 1-(3-Bromo-2-thienyl)ethanone 51863-60-6, 3',5'-Dihydroxyacetophenone 80344-24-7 89581-82-8
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation of thiadiazoline derivs. as antitumor agents)

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD.

REFERENCE(S):

(1) Awad, L; Alexandria Journal of Pharmaceutical Sciences 1989, V3(2), P119 HCAPLUS
(2) Baerbel, S; Zeitschrift fuer Chemie 1989, V29(5), P166
(3) Biogen Inc; WO 0156994 A1 2001 HCAPLUS
(4) Biogen Inc; AU 3474101 A 2001
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(8) Eli Lilly And Co; US 4338449 A 1982 HCAPLUS
(9) Farghaly, A; Arch Pharm Pharm Med Chem 2000, V333(2-3), P53 HCAPLUS
(10) Fisons Plc; EP 217519 A1 1990 HCAPLUS
(11) Fisons Plc; US 4927822 A 1990 HCAPLUS
(12) Fisons Plc; JP 62-53976 A 1990 HCAPLUS
(13) Hassan, S; J Saudi Chem Soc 1999, V3(2), P171 HCAPLUS
(14) Khalil, M; Alexandria Journal of Pharmaceutical Sciences 1989, V3(2), P221 HCAPLUS
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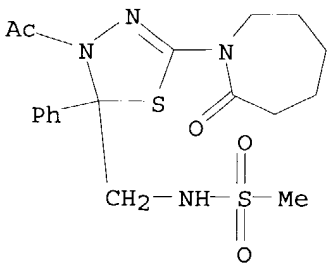
(16) Mokhtar, H; Bull Pharm Sci 1995, V18(2), P59 HCAPLUS
(17) Sumitomo Pharmaceuticals Co Ltd; JP 2000229959 A HCAPLUS
(18) Tian-Bao, H; Phosphorus, Sulfur and Silicon and the Related Elements 1997, V122, P307
(19) Warner-Lambert Co; JP 2000204077 A 2000 HCAPLUS

IT **546111-77-7P**

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(antitumor agent; preparation of thiadiazoline derivs. as antitumor agents)

RN 546111-77-7 HCAPLUS

CN 1,3,4-Thiadiazole-2-methanamine, 3-acetyl-5-(hexahydro-2-oxo-1H-azepin-1-yl)-2,3-dihydro-N-(methylsulfonyl)-2-phenyl- (9CI) (CA INDEX NAME)



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L52 ANSWER 2 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2001:502429 HCAPLUS
DOCUMENT NUMBER: 135:92553
ENTRY DATE: Entered STN: 12 Jul 2001
TITLE: Synthesis and activity of pyrroloazepine derivatives as 5-HT antagonists
INVENTOR(S): Mizuno, Akira; Shibata, Makoto; Iwamori, Tomoe; Shimamoto, Tetsuo; Nakanishi, Kyoko; Inomata, Norio
PATENT ASSIGNEE(S): Suntory Ltd., Japan
SOURCE: U.S., 54 pp., Cont.-in-part of U.S. Ser. No. 875,495. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.: A61K031-35; A61P007-00; A61P009-00
US PATENT CLASSIF.: 514215000
CLASSIFICATION: 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6258805	B1	20010710	US 1999-312713	19990517
WO 9720845	A1	19970612	WO 1996-JP3522	19961202
W: AU, CA, HU, IL, JP, KR, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5962448	A	19991005	US 1997-875495	19970821
US 2002072515	A1	20020613	US 2001-801816	20010309
US 6489473	B2	20021203		
US 2003166926	A1	20030904	US 2002-188234	20020703
US 6713634	B2	20040330		

PRIORITY APPLN. INFO.:

JP 1995-335714	A	19951201
JP 1996-46928	A	19960209
WO 1996-JP3522	W	19961202
US 1997-875495	A2	19970821
US 1999-312713	A1	19990517

US 2001-801816 A1 20010309

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 6258805	IC	A61K031-35IC A61P007-00IC A61P009-00
	NCL	514215000
US 2002072515	ECLA	C07D207/34; C07D487/04; C07D495/20
US 2003166926	ECLA	C07D207/34; C07D487/04; C07D495/20

OTHER SOURCE(S): MARPAT 135:92553

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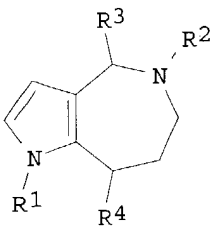

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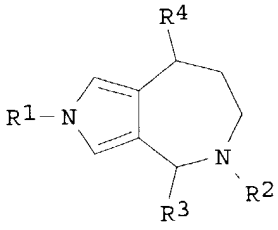

II

ABSTRACT:
Synthesis of pyrroloazepine derivs. (I) and (II) [R1 = H, alkyl, Ph, benzyl; R2 = substituted alkyl; R3,R4 independently = =O, =NOH, OH, OMe, SCH2CH2S] or pharmaceutically acceptable salts for use as 5-HT antagonists is disclosed. Thus, I (R1 = Me, R2 = (CH2)2-piperazinyl-C6H4F, R3 = =O, R4 = OH) (III) was prepared by condensation of 3-pyrrolecarboxylic acid with β-alanine Et ester hydrochloride, the amide ester saponified and the acid cyclized to pyrroloazepine with polyphosphoric acid, the azepine N alkylated with bromoalkylchloride followed by 1-(4-fluorophenyl)piperazine and reduction of carbonyl with NaBH4. III shows a 90.2% contraction at 10-7M in 5-HT action assay. I and II have strong serotonin-2 receptor antagonistic action and low toxicity and less side effects, and are therapeutically useful in the treatment of circulatory diseases and/or conditions related thereto.

SUPPL. TERM: pyrroloazepine alkyl prepn 5HT antagonists; antihypotensive circulatory disease alkylpyrroloazepine

INDEX TERM: Circulation
(disorder, treatment; synthesis and activity of pyrroloazepine derivs. as 5-HT antagonists)

INDEX TERM: 5-HT antagonists
Antihypotensives
(synthesis and activity of pyrroloazepine derivs. as 5-HT antagonists)

INDEX TERM: 191592-35-5P 191592-36-6P
ROLE: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(synthesis and activity of pyrroloazepine derivs. as 5-HT antagonists)

INDEX TERM: 191591-53-4P 191591-54-5P 191591-55-6P 191591-56-7P
191591-57-8P 191591-58-9P 191591-59-0P 191591-60-3P
191591-61-4P 191591-62-5P 191591-63-6P 191591-64-7P

191591-66-9P 191591-67-0P 191591-68-1P 191591-69-2P
191591-70-5P 191591-71-6P 191591-72-7P 191591-73-8P
191591-74-9P 191591-75-0P 191591-77-2P 191591-78-3P
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191591-85-2P 191591-86-3P 191591-87-4P 191591-88-5P
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191592-01-5P 191592-02-6P 191592-03-7P 191592-09-3P
191592-27-5P 191592-30-0P 282550-40-7P
ROLE: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(synthesis and activity of pyrroloazepine derivs. as 5-HT antagonists)

INDEX TERM: 191591-65-8P 191591-81-8P 191592-04-8P
191592-05-9P 191592-06-0P 191592-08-2P
191592-10-6P 191592-11-7P 191592-12-8P 191592-13-9P
191592-14-0P 191592-15-1P 191592-16-2P 191592-17-3P
191592-18-4P 191592-19-5P 191592-20-8P 191592-21-9P
191592-22-0P 191592-23-1P 191592-24-2P 191592-26-4P
191592-28-6P 191592-29-7P 191592-31-1P 191593-28-9P
191593-29-0P 282550-39-4P 349083-22-3P 349083-23-4P
ROLE: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and activity of pyrroloazepine derivs. as 5-HT antagonists)

INDEX TERM: 92-54-6, 1-Phenylpiperazine 109-70-6, 1-Bromo-3-chloropropane 540-63-6, 1,2-Ethanedithiol 623-47-2, Ethyl propiolate 771-99-3, 4-Phenylpiperidine 841-77-0, 1-Diphenylmethylpiperazine 922-67-8, Methyl propiolate 931-03-3, 3-Pyrrolecarboxylic acid 1011-16-1, 1-(2-Fluorophenyl)piperazine hydrochloride 2252-63-3 2262-12-6 4244-84-2, β-Alanine ethyl ester hydrochloride 5470-11-1, Hydroxylamine hydrochloride 6269-89-2, 1-(4-Nitrophenyl)piperazine 13078-12-1 27019-47-2, β-Alanine benzyl ester p-toluenesulfonate 38456-66-5, N-Formylsarcosine 38869-47-5, 1-(4-Methoxyphenyl)piperazine dihydrochloride 57238-81-0 64276-66-0, 4-Methyl-3-Pyrrolecarboxylic acid 65274-89-7 68384-82-7 78158-74-4 79144-84-6 84163-77-9 86731-89-7 94021-22-4, 1-(2-Pyrimidinyl)piperazine dihydrochloride 191592-38-8
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(synthesis and activity of pyrroloazepine derivs. as 5-HT antagonists)

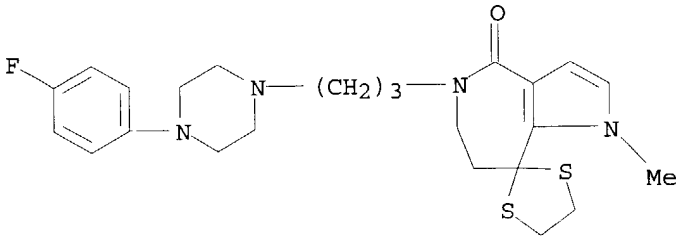
INDEX TERM: 36929-61-0P 40611-74-3P 99972-42-6P 128259-47-2P 190582-35-5P 191592-37-7P 282550-44-1P 345203-93-2P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and activity of pyrroloazepine derivs. as 5-HT antagonists)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD.

REFERENCE(S):
(1) Imoto; US 5684161 1997 HCAPLUS
(2) Mizuno; US 5206239 1993 HCAPLUS

(3) Mizuno; US 5391731 1995 HCAPLUS
(4) Mizuno; US 5397780 1995 HCAPLUS
(5) Mizuno; US 5399557 1995 HCAPLUS
(6) Mizuno; US 5416082 1995 HCAPLUS

IT **191592-05-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and activity of pyrroloazepine derivs. as 5-HT antagonists)
RN 191592-05-9 HCAPLUS
CN Spiro[1,3-dithiolane-2,8'(1'H)-pyrrolo[3,2-c]azepin]-4'(5'H)-one, 5'-[3-[4-(4-fluorophenyl)-1-piperazinyl]propyl]-6',7'-dihydro-1'-methyl- (9CI) (CA INDEX NAME)



L52 ANSWER 3 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 1997:461620 HCAPLUS
DOCUMENT NUMBER: 127:81465
ENTRY DATE: Entered STN: 24 Jul 1997
TITLE: Preparation of pyrroloazepine derivatives as serotonin-2 receptor antagonists
INVENTOR(S): Mizuno, Akira; Shibata, Makoto; Iwamori, Tomoe; Shimamoto, Tetsuo; Nakanishi, Kyoko; Inomata, Norio
PATENT ASSIGNEE(S): Suntory Limited, Japan
SOURCE: PCT Int. Appl., 160 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
INT. PATENT CLASSIF.:
MAIN: C07D487-04
SECONDARY: A61K031-55
CLASSIFICATION: 28-17 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9720845	A1	19970612	WO 1996-JP3522	19961202
W: AU, CA, HU, IL, JP, KR, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2212092	AA	19970612	CA 1996-2212092	19961202
AU 9676558	A1	19970627	AU 1996-76558	19961202
AU 719230	B2	20000504		
EP 807632	A1	19971119	EP 1996-939340	19961202
EP 807632	B1	20020417		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, FI				
IL 121432	A1	20000928	IL 1996-121432	19961202
AT 216388	E	20020515	AT 1996-939340	19961202
ES 2179218	T3	20030116	ES 1996-939340	19961202
JP 3563076	B2	20040908	JP 1997-521152	19961202
US 5962448	A	19991005	US 1997-875495	19970821
US 6258805	B1	20010710	US 1999-312713	19990517
US 2002072515	A1	20020613	US 2001-801816	20010309
US 6489473	B2	20021203		
US 2003166926	A1	20030904	US 2002-188234	20020703
US 6713634	B2	20040330		

PRIORITY APPLN. INFO.:

JP 1995-335714	A	19951201
JP 1996-46928	A	19960209
WO 1996-JP3522	W	19961202
US 1997-875495	A2	19970821
US 1999-312713	A1	19990517
US 2001-801816	A1	20010309

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9720845	ICM	C07D487-04
	ICS	A61K031-55
US 2002072515	ECLA	C07D207/34; C07D487/04; C07D495/20
US 2003166926	ECLA	C07D207/34; C07D487/04; C07D495/20

OTHER SOURCE(S): MARPAT 127:81465

GRAPHIC IMAGE:

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

ABSTRACT:
The title compds. [I; ring P = (un)substituted pyrrole ring; A = alkylene, alkenylene, alkynylene; Y = N-containing heterocyclyl, etc; Z1, E2 = H, lower alkyl; dotted line = bond or none] are prepared I, having a potent serotonin-2 receptor antagonism, are reduced in toxicity and side effects, and are useful as therapeutic agents for circulatory diseases such as ischemic heart diseases, cerebrovascular disorders, and peripheral circulatory disturbances. Thus, pyrroloazepine derivative (II) (preparation given) was reacted with HSCH2CH2SH in the
presence of BF3.Et2O in AcOH to give 79% the title compound (III), which at 10-8 M showed 75.5% inhibitory activity against serotonin (5-HT).

SUPPL. TERM: pyrroloazepine prepn serotonin receptor antagonist; circulatory disease treatment pyrroloazepine prepn; ischemic heart disease treatment pyrroloazepine prepn; cerebrovascular disorder treatment pyrroloazepine prepn; peripheral circulatory disturbance treatment pyrroloazepine prepn

INDEX TERM: Brain, disease
(cerebrovascular; preparation of pyrroloazepine derivs. as therapeutic agents for circulatory diseases such as ischemic heart diseases, cerebrovascular disorders, and peripheral circulatory disturbances)

INDEX TERM: 5-HT receptors
Tumor necrosis factors
ROLE: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)

(preparation of pyrroloazepine derivs. as serotonin-2 receptor antagonists)

INDEX TERM: Heart, disease
(preparation of pyrroloazepine derivs. as therapeutic agents for circulatory diseases such as ischemic heart diseases, cerebrovascular disorders, and peripheral circulatory disturbances)

INDEX TERM:

191591-53-4P	191591-54-5P	191591-55-6P	191591-56-7P
191591-57-8P	191591-58-9P	191591-59-0P	191591-60-3P
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191591-77-2P	191591-78-3P	191591-80-7P	191591-81-8P
191591-82-9P	191591-83-0P	191591-84-1P	191591-85-2P
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191592-25-3P	191592-26-4P	191592-27-5P	191592-28-6P
191592-29-7P	191592-30-0P	191592-31-1P	191592-32-2P
191592-33-3P	191592-34-4P	191592-35-5P	191592-36-6P
191593-28-9P	191593-29-0P		

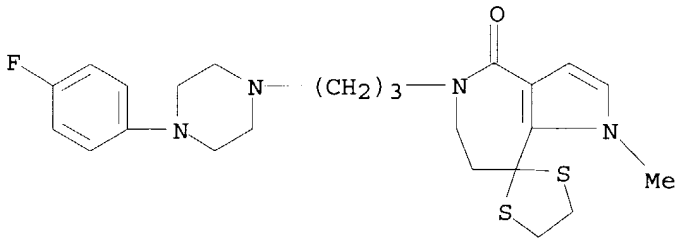
ROLE: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrroloazepine derivs. as serotonin-2 receptor antagonists)

INDEX TERM: 74-88-4, Methyl iodide, reactions 92-54-6, 1-Phenylpiperazine 100-39-0, Benzyl bromide 101-83-7, Dicyclohexylamine 105-37-3, Ethyl propanoate 109-70-6, 1-Bromo-3-chloropropane 540-63-6, 1,2-Ethanedithiol 554-12-1, Methyl propanoate 771-99-3, 4-Phenylpiperidine 841-77-0, 1-Diphenylmethylpiperazine 1011-16-1, 1-(2-Fluorophenyl)piperazine hydrochloride 2252-63-3, 1-(4-Fluorophenyl)piperazine 2262-12-6 4244-84-2, β-Alanine ethyl ester hydrochloride 6269-89-2, 1-(4-Nitrophenyl)piperazine 6652-06-8 6940-78-9, 1-Bromo-4-chlorobutane 13078-12-1 25519-78-2, 4-(4-Fluorobenzoyl)piperidine hydrochloride 38456-66-5, N-Formylsarcosine 38869-47-5, 1-(4-Methoxyphenyl)piperazine dihydrochloride 42854-62-6 65274-89-7 78158-74-4 79144-84-6 84163-68-8 86731-89-7 94021-22-4, 1-(2-Pyrimidinyl)piperazine dihydrochloride 191592-38-8
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation of pyrroloazepine derivs. as serotonin-2 receptor antagonists)

INDEX TERM: 36929-61-0P 40611-74-3P 99972-42-6P 128259-47-2P 190582-35-5P 191592-37-7P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of pyrroloazepine derivs. as serotonin-2 receptor

antagonists)

IT **191592-05-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrroloazepine derivs. as serotonin-2 receptor antagonists)
RN 191592-05-9 HCAPLUS
CN Spiro[1,3-dithiolane-2,8'(1'H)-pyrrolo[3,2-c]azepin]-4'(5'H)-one, 5'-[3-[4-(4-fluorophenyl)-1-piperazinyl]propyl]-6',7'-dihydro-1'-methyl- (9CI) (CA INDEX NAME)



L52 ANSWER 4 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 1997:640247 HCAPLUS
DOCUMENT NUMBER: 127:318890
ENTRY DATE: Entered STN: 09 Oct 1997
TITLE: Benzo-fused lactams promoting release of growth hormone
INVENTOR(S): Wyvratt, Matthew; Devita, Robert; Bochis, Richard; Schoen, William
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: U.S., 76 pp., Cont.-in-part of U.S. 5,283,241.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.:
MAIN: A61K031-55
SECONDARY: C07D209-34; C07D215-227; C07D223-16
US PATENT CLASSIF.: 514183000
CLASSIFICATION: 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 2, 17, 63
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5672596	A	19970930	US 1995-392961	19950418
US 5283241	A	19940201	US 1992-936975	19920828
WO 9405634	A1	19940317	WO 1993-US7791	19930818
W: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5968924	A	19991019	US 1997-820302	19970318

PRIORITY APPLN. INFO.:
US 1992-936975 A2 19920828
WO 1993-US7791 W 19930818
US 1995-392961 A3 19950418

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 5672596	ICM	A61K031-55
	ICS	C07D209-34; C07D215-227; C07D223-16
	NCL	514183000

OTHER SOURCE(S): MARPAT 127:318890
GRAPHIC IMAGE:

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

ABSTRACT:
There are disclosed certain novel benzo-fused lactams I [Ar = (un)substituted Ph; L = (un)substituted C6H4; m = 0, 1; p = 0-3; q = 0-4; X = bond, CO, O, S, S(O), S(O)2, CH(OH), (un)substituted NH, CH:CH; R1, R2 = H, halo, alkyl, perfluoroalkyl, cyano, NO2, (un)substituted Ph, etc.; R4, R5 = (un)substituted alk(en/yn)yl or Ph; or R4R5 = alkylene chain with optional heteroat. interruptions; R6 = H, alkyl, Ph, or phenylalkyl; A = alkylene chain with optional substituents or spirocyclic alkylene fusion]. The compds. promote the release of growth hormone in humans and animals (no data). This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to increase the stature of those afflicted with a lack of a normal secretion of natural growth hormone. Growth promoting compns. containing I as active ingredients are also disclosed. Approx. 60 synthetic examples with characterizing phys. data are given. For instance, amidation of 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one with 3-[(tert-butoxycarbonyl)amino]-3-methylbutanoic acid (prepns. given) using the reagents BOP and Et3N (94%), followed by N-alkylation in the 1-position with 4-(bromomethyl)-2'-[(methoxycarbonyl)amino]-1,1'-biphenyl using NaH in DMF (63%), and deprotection with CF3CO2H (96%), gave title compound II as the trifluoroacetate salt.

SUPPL. TERM: benzo lactam growth hormone release promoter; benzazepine prepn growth hormone release promoter

INDEX TERM: Antiobesity agents
(preparation of benzo-fused lactams as growth hormone release promoters)

INDEX TERM: Growth factors, animal
ROLE: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); MSC (Miscellaneous); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); USES (Uses)
(preparation of benzo-fused lactams as growth hormone release promoters)

INDEX TERM: Osteoporosis
(therapeutic agents; preparation of benzo-fused lactams as growth hormone release promoters)

INDEX TERM: Adrenoceptor agonists
(α2-, compns. containing; preparation of benzo-fused lactams as growth hormone release promoters)

INDEX TERM: Adrenoceptor agonists
(β3-, compns. containing; preparation of benzo-fused lactams as growth hormone release promoters)

INDEX TERM: 114343-29-2P 169188-17-4P, 2'-Nitro-1,1'-biphenyl-4-carboxaldehyde

ROLE: BYP (Byproduct); PREP (Preparation)
(byproduct; preparation of benzo-fused lactams as growth hormone release promoters)

INDEX TERM: 32980-26-0P, 2,2-Dimethylbutanedioic acid 1-methyl ester 160278-46-6P 197652-82-7P, 4-(Dibromomethyl)-2'-nitro-1,1'-biphenyl
ROLE: BYP (Byproduct); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(byproduct; preparation of benzo-fused lactams as growth hormone release promoters)

INDEX TERM: 9002-64-6, Parathyroid hormone 9034-39-3, Somatoliberin 15477-76-6D, Phosphonate, derivs. 36085-73-1, B-HT 920 67763-96-6, IGF-1 67763-97-7, IGF-2 87616-84-0 141925-59-9, GHRP-1 158861-67-7, GHRP-2
ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. containing; preparation of benzo-fused lactams as growth hormone release promoters)

INDEX TERM: 937-12-2P, (4-Methylphenyl)trimethylstannane 3349-64-2P, 1-Tetralone oxime 4424-80-0P, 2,3,4,5-Tetrahydro-1H-1-benzazepin-2-one 4879-95-2P, 4,4-Dimethylazetidin-2-one 16927-79-0P 51219-55-7P, 3-[[(Benzyloxy)carbonyl]amino]-3-methylbutanoic acid 54043-71-9P, 2,2-Dimethylbutanedioic acid 4-methyl ester 70680-21-6P, 4-Methyl-2'-nitro-1,1'-biphenyl 86499-35-6P, 3-Amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one 101043-55-4P, 4-Methyl-2'-hydroxy-1,1'-biphenyl 114772-39-3P, 4-(Bromomethyl)-2'-nitro-1,1'-biphenyl 114772-53-1P, 4'-Methyl-1,1'-biphenyl-2-carbonitrile 128182-82-1P, 3-[[(Benzyloxy)carbonyl]amino]-3-methylbutanoic acid methyl ester 129765-95-3P, 3-[(tert-Butoxycarbonyl)amino]-3-methylbutanoic acid 133776-42-8P, 4-Bromobenzyl tert-butyldiphenylsilyl ether 135689-84-8P, 3'-Bromo-4'-methyl-1,1'-biphenyl-2-carbonitrile 135689-85-9P, 3'-Bromo-4'-(bromomethyl)-1,1'-biphenyl-2-carbonitrile 137036-55-6P, (R)-3-Amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one 140700-64-7P, 3-Iodo-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one 145457-70-1P 145485-03-6P 145485-77-4P 145486-16-4P 145486-21-1P, 4-Methyl-2'-acetoxy-1,1'-biphenyl 145486-22-2P, 4-(Bromomethyl)-2'-acetoxy-1,1'-biphenyl 145486-23-3P 145486-24-4P, 4-Methyl-2'-(4-nitrophenoxy)-1,1'-biphenyl 145486-25-5P, 4-(Bromomethyl)-2'-(4-nitrophenoxy)-1,1'-biphenyl 145486-26-6P 145486-32-4P 145486-33-5P 145486-45-9P 145486-47-1P 145486-75-5P 148289-82-1P, [4-[[(tert-Butyldiphenylsilyl)oxy]methyl]phenyl]boronic acid 155300-46-2P, N-(tert-Butoxycarbonyl)-4,4-dimethylazetidin-2-one 159815-76-6P, 4-(Hydroxymethyl)-2'-nitro-1,1'-biphenyl 159815-77-7P 159815-78-8P 159815-79-9P 159815-80-2P 159815-81-3P 159815-82-4P 159815-83-5P 159815-84-6P 159815-85-7P 159815-86-8P 159815-87-9P 159815-88-0P 159815-89-1P 159815-90-4P 159815-92-6P 159815-93-7P 159815-95-9P 159815-96-0P 159815-97-1P, 4-Methyl-2'-(2-nitrophenoxy)-1,1'-biphenyl 159815-98-2P, 4-(Bromomethyl)-2'-(2-nitrophenoxy)-1,1'-biphenyl 159815-99-3P 159816-01-0P 160278-26-2P 162356-90-3P, N-(tert-Butoxycarbonyl)-2-bromobenzylamine 162356-92-5P 162356-93-6P 168059-24-3P 169188-18-5P 195248-05-6P 195248-06-7P 195248-07-8P 195248-08-9P 197652-11-2P 197652-13-4P 197652-15-6P 197652-17-8P

197652-19-0P 197652-21-4P 197652-23-6P 197652-25-8P
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197652-42-9P 197652-43-0P 197652-44-1P 197652-45-2P
197652-46-3P 197652-47-4P 197652-48-5P,
3'-Bromo-4'-(acetoxymethyl)-1,1'-biphenyl-2-carbonitrile
197652-49-6P, 3'-Bromo-4'-(hydroxymethyl)-1,1'-biphenyl-2-carbonitrile 197652-50-9P 197652-51-0P 197652-52-1P
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197652-57-6P 197652-58-7P 197652-59-8P,
2'-(2-Aminoethyl)-1,1'-biphenyl-4-methanol 197652-60-1P
197652-61-2P 197652-62-3P 197652-63-4P 197652-64-5P
197652-65-6P 197652-66-7P 197652-67-8P 197652-68-9P
197652-69-0P 197652-70-3P 197652-71-4P 197652-73-6P
197652-74-7P 197652-75-8P 197652-76-9P 197652-77-0P
197652-78-1P 197652-79-2P 197652-80-5P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of benzo-fused lactams as growth hormone release promoters)

INDEX TERM: 7727-37-9, Nitrogen, biological studies
ROLE: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism; treatment of nitrogen wasting; preparation of benzo-fused lactams as growth hormone release promoters)

INDEX TERM: 159814-84-3P 159814-90-1P 159814-92-3P 159814-96-7P
ROLE: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of benzo-fused lactams as growth hormone release promoters)

INDEX TERM: 159814-82-1P 159814-86-5P 159814-88-7P 159814-94-5P
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197651-93-7P 197651-96-0P 197651-98-2P 197652-00-9P
197652-02-1P 197652-04-3P 197652-06-5P 197652-08-7P
ROLE: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzo-fused lactams as growth hormone release promoters)

INDEX TERM: 9002-72-6, Growth hormone
ROLE: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); MSC (Miscellaneous); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(preparation of benzo-fused lactams as growth hormone release promoters)

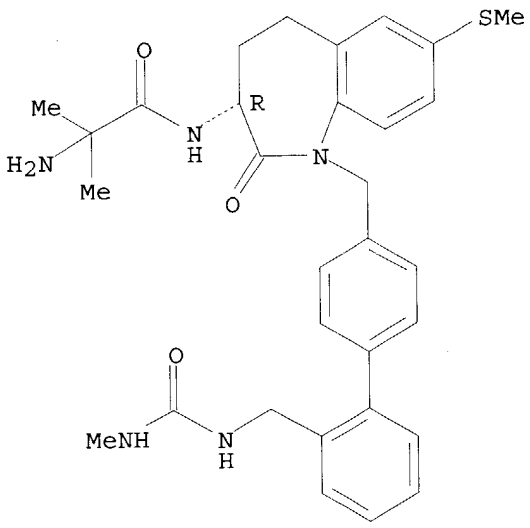
INDEX TERM: 62-53-3, Benzenamine, reactions 100-46-9, Benzylamine, reactions 110-78-1, 1-Propyl isocyanate 110-85-0, Piperazine, reactions 110-91-8, Morpholine, reactions 115-11-7, Isobutylene, reactions 350-46-9, 1-Fluoro-4-nitrobenzene 529-34-0, 1-Tetralone 577-19-5, 2-Bromo-1-nitrobenzene 597-43-3, 2,2-Dimethylsuccinic acid 623-33-6, Glycine ethyl ester hydrochloride 700-87-8, 2-Methoxyphenyl isocyanate 873-75-6, 4-Bromobenzyl alcohol 1189-71-5, Chlorosulfonyl isocyanate 1493-27-2, 1-Fluoro-2-nitrobenzene 1795-48-8, Isopropyl isocyanate 2042-37-7, 2-Bromobenzonitrile 2142-69-0, 2'-Bromoacetophenone 2462-31-9, Glycine benzyl ester hydrochloride 3173-56-6, Benzyl isocyanate 4294-57-9, p-Tolylmagnesium bromide 5465-63-4, 2-Bromobenzylamine hydrochloride 5720-05-8, 4-Tolylboronic acid 13139-17-8, N-[[(Benzyloxy)carbonyl]oxy]succinimide 15030-72-5, N-(Carbobenzyloxy)-2-methylalanine 15159-40-7, 4-Morpholinocarbonyl chloride 15186-48-8, D-Glyceraldehyde acetonide 19472-74-3, 2-Bromophenylacetonitrile 27532-96-3, Glycine tert-butyl ester hydrochloride 30674-80-7 30992-29-1, N-(tert-Butoxycarbonyl)-2-methylalanine 81445-45-6, (R)-2-Benzyloxypropanal 87037-69-2, (R)-2-Benzyloxy-1-propanol 96289-09-7 114772-54-2, 4'-(Bromomethyl)-1,1'-biphenyl-2-carbonitrile 197652-81-6
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(starting material; preparation of benzo-fused lactams as growth hormone release promoters)

IT **197651-01-7P 197651-05-1P 197651-09-5P**
197651-13-1P 197651-17-5P 197651-22-2P
197651-27-7P 197651-32-4P 197651-36-8P
197651-41-5P 197651-47-1P 197651-52-8P

197651-56-2P 197651-61-9P 197651-74-4P
197651-87-9P
RL: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzo-fused lactams as growth hormone release promoters)

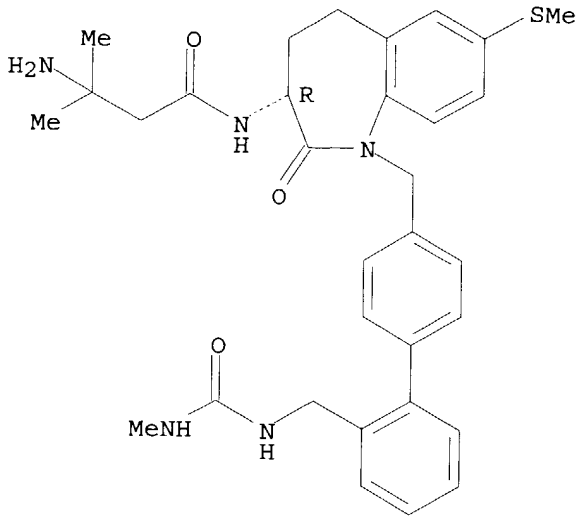
RN 197651-01-7 HCAPLUS
CN Propanamide, 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[(methylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



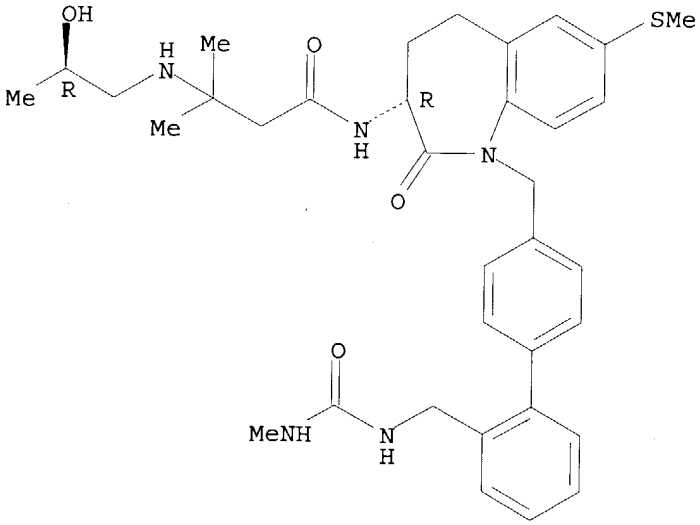
RN 197651-05-1 HCAPLUS
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[(methylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



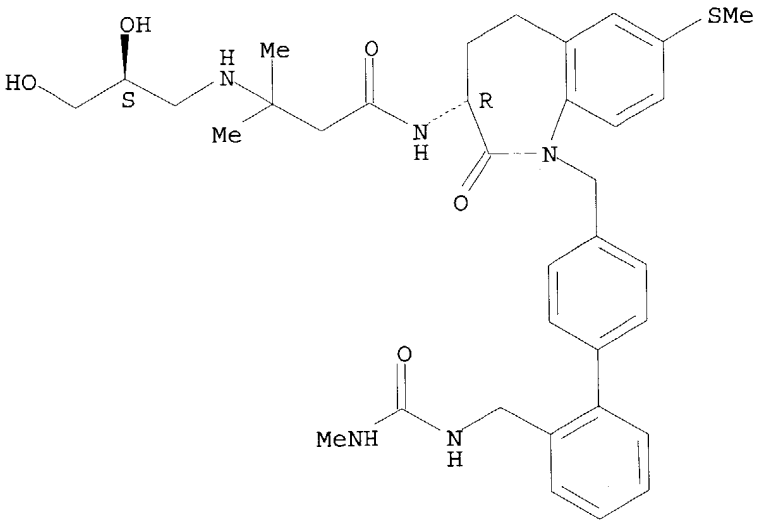
RN 197651-09-5 HCAPLUS
CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[(methylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



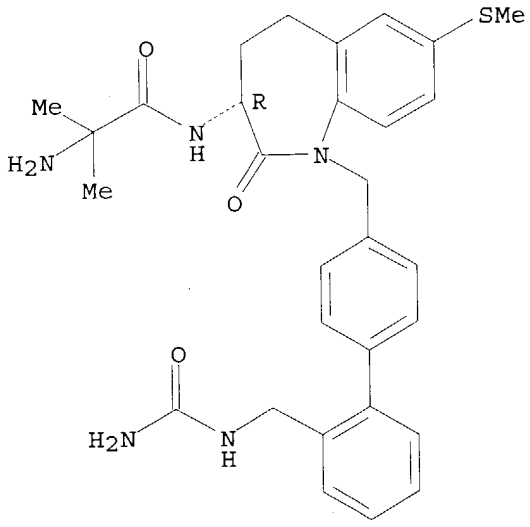
RN 197651-13-1 HCAPLUS
CN Butanamide, 3-[(2,3-dihydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[(methylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



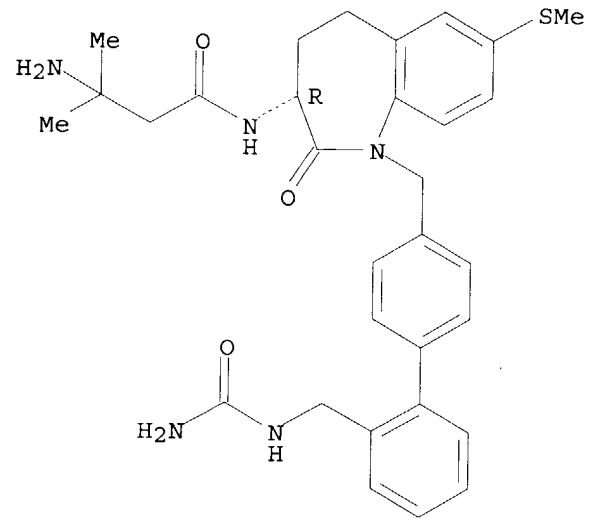
RN 197651-17-5 HCAPLUS
CN Propanamide, 2-amino-N-[1-[[2'-[[(aminocarbonyl)amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-2-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



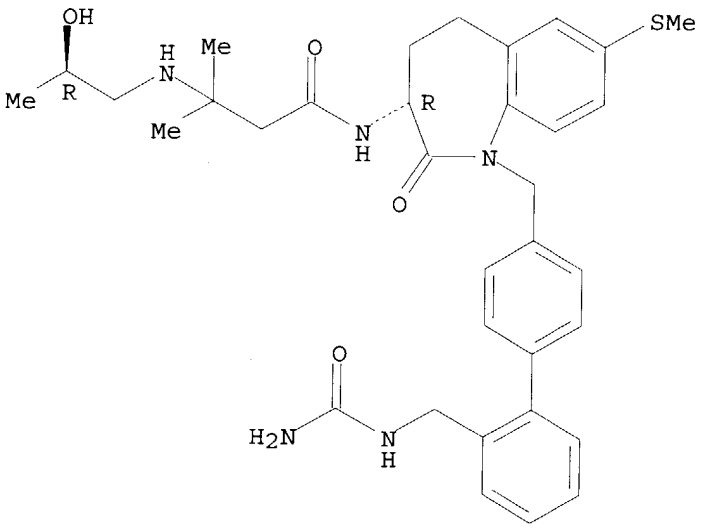
RN 197651-22-2 HCAPLUS
CN Butanamide, 3-amino-N-[1-[[2'-[[(aminocarbonyl)amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



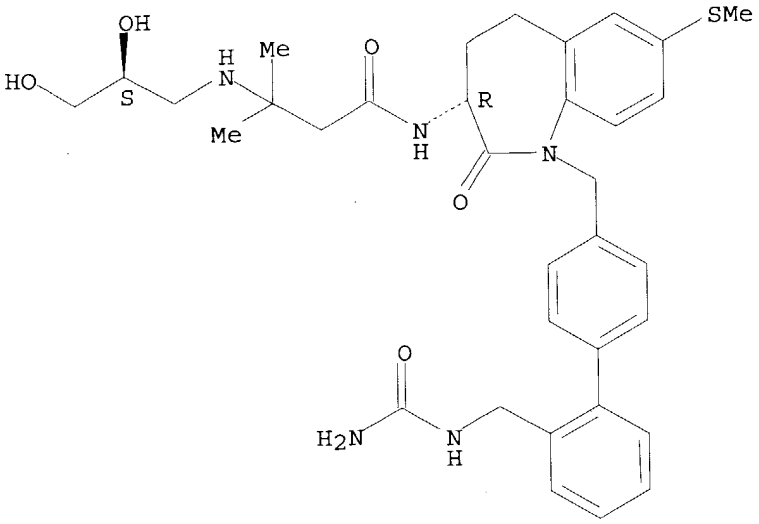
RN 197651-27-7 HCAPLUS
CN Butanamide, N-[1-[[2'-[[(aminocarbonyl)amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-[(2-hydroxypropyl)amino]-3-methyl-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



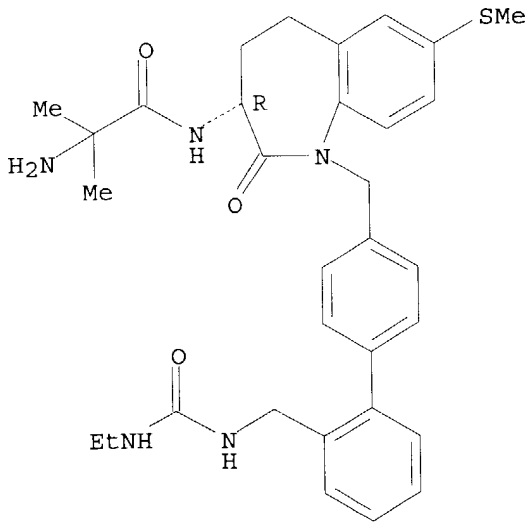
RN 197651-32-4 HCAPLUS
CN Butanamide, N-[1-[[2'-[[(aminocarbonyl)amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-[(2,3-dihydroxypropyl)amino]-3-methyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



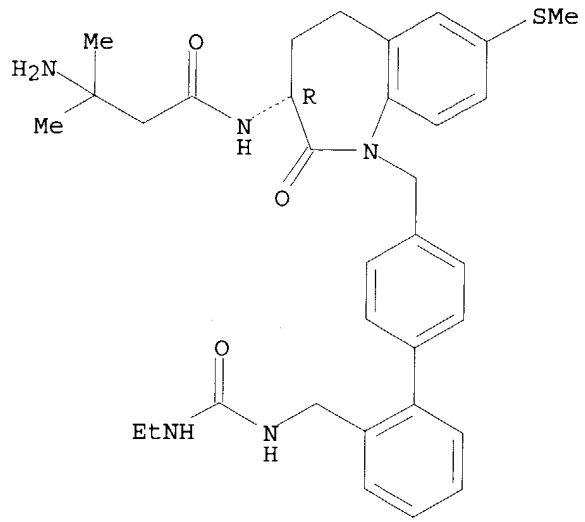
RN 197651-36-8 HCAPLUS
CN Propanamide, 2-amino-N-[1-[[2'-[[[(ethylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-2-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



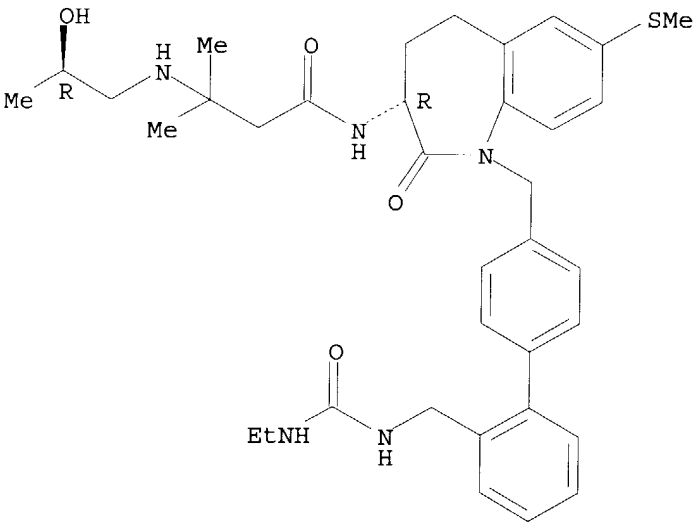
RN 197651-41-5 HCAPLUS
CN Butanamide, 3-amino-N-[1-[[2'-[[[(ethylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



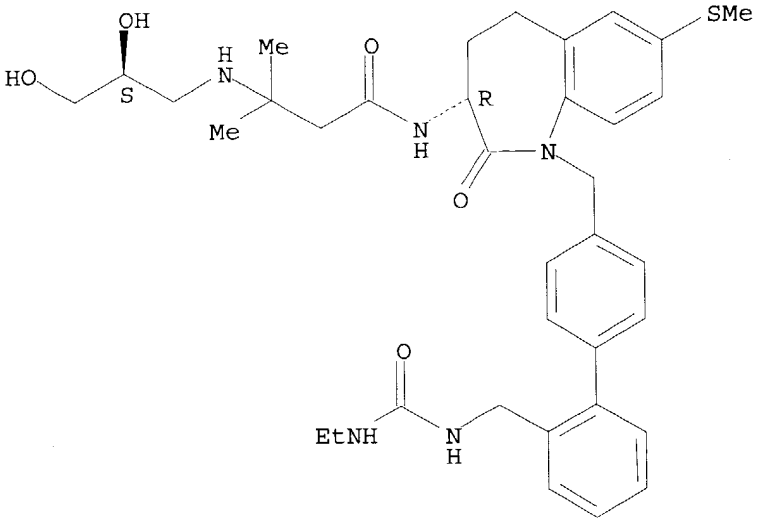
RN 197651-47-1 HCAPLUS
CN Butanamide, N-[1-[[2'-[[[(ethylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-[(2-hydroxypropyl)amino]-3-methyl-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



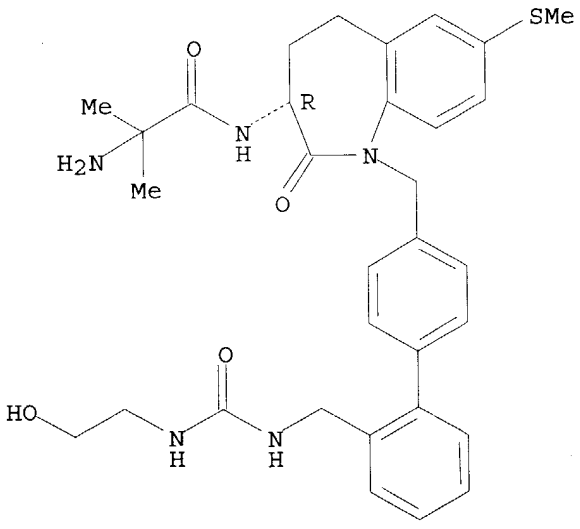
RN 197651-52-8 HCAPLUS
CN Butanamide, 3-[(2,3-dihydroxypropyl)amino]-N-[1-[[2'-[[[(ethylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-methyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



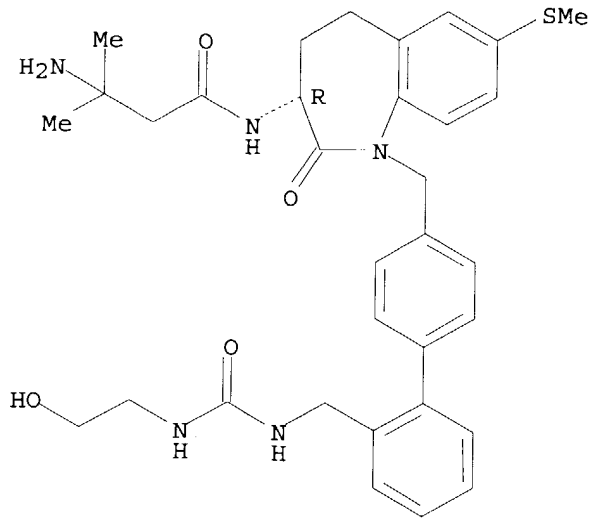
RN 197651-56-2 HCAPLUS
CN Propanamide, 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[[(2-hydroxyethyl)amino]carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



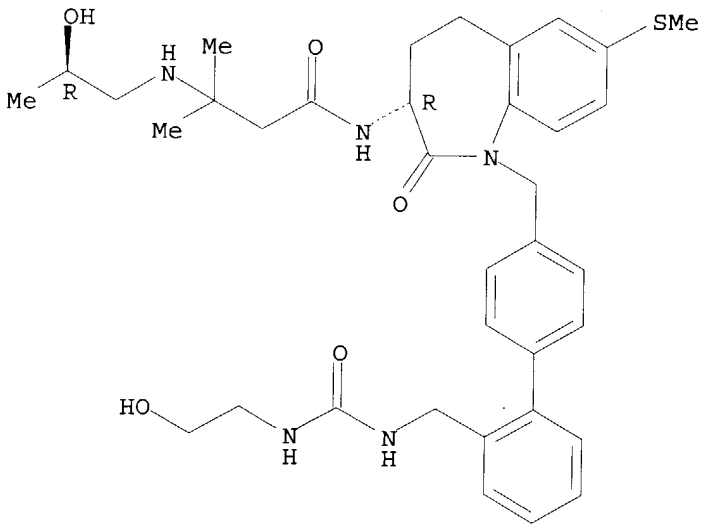
RN 197651-61-9 HCAPLUS
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[[(2-hydroxyethyl)amino]carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



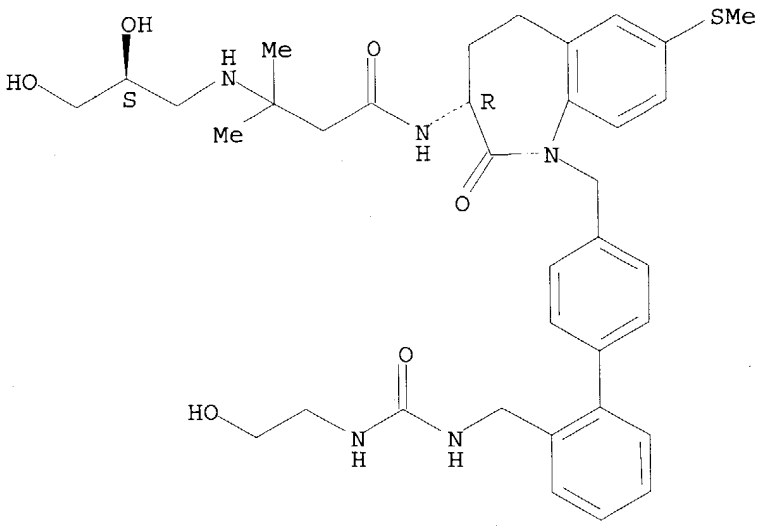
RN 197651-74-4 HCAPLUS
CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[[(2-hydroxyethyl)amino]carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 197651-87-9 HCAPLUS
CN Butanamide, 3-[(2,3-dihydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[[(2-hydroxyethyl)amino]carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L52 ANSWER 5 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:902362 HCAPLUS
DOCUMENT NUMBER: 141:379928
ENTRY DATE: Entered STN: 28 Oct 2004
TITLE: Preparation of thiadiazoline derivatives as M-stage kinesin inhibitors
INVENTOR(S): Murakata, Chikara; Yamashita, Yoshinori; Nakai, Ryuichiro; Akasaka, Kazuto; Ino, Yoji; Kato, Kazuhiko; Kitamura, Yuji
PATENT ASSIGNEE(S): Kyowa Hakko Kogyo Co., Ltd., Japan; Fuji Photo Film Co., Ltd.
SOURCE: PCT Int. Appl., 198 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
INT. PATENT CLASSIF.:
MAIN: C07D285-12
SECONDARY: C07D417-04; C07D417-12; A61K031-433; A61K031-4439; A61K031-5377; A61K031-506; A61P009-04; A61P009-10; A61P019-02; A61P037-02
CLASSIFICATION: 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004092147	A1	20041028	WO 2004-JP5489	20040416

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,

ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: JP 2003-114071 A 20030418
JP 2003-164727 A 20030610

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004092147	ICM	C07D285-12
	ICS	C07D417-04; C07D417-12; A61K031-433; A61K031-4439; A61K031-5377; A61K031-506; A61P009-04; A61P009-10; A61P019-02; A61P037-02

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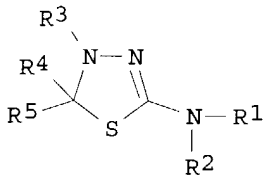

I

ABSTRACT:
The title compds. I [R1 represents hydrogen, etc.; R2 represents hydrogen, C(:W)R6 (wherein W represents oxygen or sulfur and R6 represents (un)substituted lower alkyl, etc.), etc.; R3 represents C(:Z)R19 (wherein Z represents oxygen or sulfur and R19 represents (un)substituted lower alkyl, etc.) etc.; R4 represents (un)substituted lower alkyl, etc.; and R5 represents (un)substituted aryl, etc.] are prepared I [R1 = H; R2 = R3 = COCMe3; R4 = (CH2)2NH(CH2)2Me; R5 = phenyl] was prepared in a multistep process starting from thiosemicarbazide hydrochloride and Et benzoylacetate. Compds. of this invention in vitro showed IC50 values of ≤ 2 μmol/L against Eg5 ATPase. Formulations are given.

SUPPL. TERM: thiadiazoline deriv prepn M stage kinesin inhibitor

INDEX TERM: Kinesins
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(M stage, Eg5; preparation of thiadiazoline derivs. as M-stage kinesin inhibitors)

INDEX TERM: Human
(preparation of thiadiazoline derivs. as M-stage kinesin inhibitors)

INDEX TERM: 9000-83-3, ATPase
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(Eg5; preparation of thiadiazoline derivs. as M-stage kinesin inhibitors)

INDEX TERM: 781675-01-2P 781675-03-4P 781675-06-7P 781675-10-3P
781675-13-6P 781675-16-9P 781675-17-0P 781675-18-1P
781675-22-7P 781675-25-0P 781675-28-3P 781675-46-5P
781675-50-1P 781675-51-2P 781675-52-3P 781675-63-6P
781675-64-7P 781675-67-0P 781675-68-1P 781675-69-2P
781675-70-5P
ROLE: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of thiadiazoline derivs. as M-stage kinesin inhibitors)

INDEX TERM: 781674-99-5P 781675-00-1P 781675-02-3P 781675-04-5P
781675-05-6P 781675-07-8P 781675-08-9P 781675-09-0P
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781675-76-1P 781675-77-2P 781675-78-3P 781675-79-4P
781675-80-7P 781675-81-8P
ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of thiadiazoline derivs. as M-stage kinesin inhibitors)

INDEX TERM: 50-00-0, Formalin, reactions 57-06-7, Allylisothiocyanate 67-64-1, Acetone, reactions 74-88-4, Methyl iodide, reactions 74-89-5, Methylamine, reactions 75-03-6, Ethyl iodide 75-04-7, Ethylamine, reactions 75-07-0, Acetaldehyde, reactions 75-36-5, Acetyl chloride 78-81-9, Isobutylamine 79-03-8, Propionyl chloride 79-04-9, Chloroacetyl chloride 79-19-6, Thiosemicarbazide 79-30-1, Isobutyryl chloride 79-44-7, Dimethylcarbamoyl chloride 83-33-0, 1-Indanone 88-15-3, 2-Acetylthiophene 89-74-7, 2',4'-Dimethylacetophenone 93-08-3, 2'-Acetonaphthone 93-55-0, Propiophenone 94-02-0, Ethyl benzoylacetate 97-72-3, Isobutyric anhydride 98-86-2, Acetophenone, reactions 99-02-5, 3'-Chloroacetophenone 99-91-2, 4'-Chloroacetophenone 99-93-4, 4'-Hydroxyacetophenone 100-06-1, 4'-Methoxyacetophenone 100-19-6, 4'-Nitroacetophenone 100-39-0, Benzyl bromide 100-83-4, 3-Hydroxybenzaldehyde 107-08-4, Propyl iodide 107-10-8, Propylamine, reactions 108-24-7, Acetic anhydride 108-91-8, Cyclohexylamine, reactions 109-73-9, Butylamine, reactions 109-83-1, 2-(Methylamino)ethanol 109-89-7, Diethylamine, reactions 109-90-0, Ethylisocyanate 110-89-4, Piperidine, reactions 110-91-8, Morpholine, reactions 111-42-2, Diethanolamine, reactions 111-95-5 115-69-5, 2-Amino-2-methyl-1,3-propanediol 118-93-4, 2'-Hydroxyacetophenone 119-61-9, Benzophenone, reactions 121-71-1, 3'-Hydroxyacetophenone 121-89-1, 3'-Nitroacetophenone 122-00-9, 4'-Methylacetophenone 122-57-6, Benzylideneacetone 123-62-6, Propionic anhydride 124-40-3, Dimethylamine, reactions 124-63-0, Methanesulfonyl chloride 141-43-5, Ethanolamine, reactions 142-61-0, Hexanoyl chloride 302-01-2, Hydrazine, reactions 349-76-8, 3'-Trifluoromethylacetophenone 350-03-8, 3-Acetylpyridine 373-88-6, 2,2,2-Trifluoroethylamine hydrochloride 403-42-9, 4'-Fluoroacetophenone 445-27-2, 2'-Fluoroacetophenone 455-36-7, 3'-Fluoroacetophenone 497-38-1, 2-Norbornanone 502-56-7, 5-Nonanone 529-34-0,

α-Tetralone 530-93-8, β-Tetralone 540-80-7, tert-Butyl nitrite 577-16-2, 2'-Methylacetophenone 577-56-0, 2-Acetylbenzoic acid 577-59-3, 2'-Nitroacetophenone 579-74-8, 2'-Methoxyacetophenone 585-74-0, 3'-Methylacetophenone 586-37-8, 3'-Methoxyacetophenone 591-78-6, 2-Hexanone 594-44-5, Ethanesulfonyl chloride 611-70-1 616-30-8, 3-Amino-1,2-propanediol 624-78-2, Ethylmethylamine 626-58-4, 4-Methylpiperidine 765-30-0, Cyclopropylamine 927-58-2, 4-Bromobutyryl chloride 936-59-4, 3-Chloropropiophenone 941-98-0, 1'-Acetonaphthone 1001-53-2, N-Acetylethylenediamine 1009-14-9 1072-83-9, 2-Acetylpyrrole 1117-97-1, N,O-Dimethylhydroxylamine 1122-54-9, 4-Acetylpyridine 1122-62-9, 2-Acetylpyridine 1192-62-7, 2-Acetylfuran 1197-09-7, 3',4'-Dihydroxyacetophenone 1443-80-7, 4-Acetylbenzonitrile 1468-83-3, 3-Acetylthiophene 1501-04-8, 4-Carbomethoxybutyrophenone 1501-26-4, Methyl 4-(chloroformyl)butyrate 1579-15-3, 2-Acetoxy-1-indanone 1622-32-8, 2-Chloroethanesulfonyl chloride 1633-82-5, 3-Chloropropanesulfonyl chloride 1668-10-6, Glycinamide hydrochloride 1762-95-4, Ammonium thiocyanate 2040-04-2, 2',6'-Dimethoxyacetophenone 2051-95-8, 3-Benzoylpropionic acid 2142-68-9, 2'-Chloroacetophenone 2142-69-0, 2'-Bromoacetophenone 2550-26-7, Benzylacetone 3144-09-0, Methanesulfonamide 3282-30-2, Trimethylacetyl chloride 3303-84-2, N-tert-Butoxycarbonyl-β-alanine 3481-02-5 3506-36-3, 3-Dimethylaminopropiophenone 3518-65-8, Chloromethanesulfonyl chloride 3731-51-9, 2-(Aminomethyl)pyridine 3731-53-1, 4-Picolylamine 4023-34-1, Cyclopropanecarbonyl chloride 4079-52-1, 2-Methoxyacetophenone 4224-70-8, 6-Bromohexanoic acid 4244-84-2 4509-90-4, 5-Bromovaleryl chloride 4524-93-0, Cyclopentanecarbonyl chloride 4530-20-5, N-tert-Butoxycarbonylglycine 5351-77-9 5370-25-2 5468-37-1, 2-Aminoacetophenone hydrochloride 5470-11-1 5680-79-5 6136-68-1, 3-Acetylbenzonitrile 6610-29-3, 4-Methylthiosemicarbazide 6638-79-5, N,O-Dimethylhydroxylamine hydrochloride 7664-41-7, Ammonia, reactions 7778-42-9, Sulfamoyl chloride 10487-71-5, Crotonoyl chloride 13360-57-1, Dimethylsulfamoyl chloride 13431-34-0, 4-Ethylthiosemicarbazide 13679-72-6, 2-Acetyl-3-methylthiophene 15183-93-4, Thiosemicarbazide hydrochloride 16819-79-7 19172-47-5, Lawesson's reagent 22047-25-2, Acetylpyrazine 22720-75-8 22809-37-6, 6-Bromohexanoyl chloride 24295-03-2, 2-Acetylthiazole 24424-99-5, Di-tert-butyl dicarbonate 25333-24-8 26628-22-8, Sodium azide 26976-88-5 38870-89-2, Methoxyacetyl chloride 40635-66-3, 2-Acetoxyisobutyryl chloride 42471-59-0, 1-Bromo-3(methoxymethoxy)benzene 51863-60-6, 3',5'-Dihydroxyacetophenone 57260-73-8, tert-Butyl-N-(2-aminoethyl)carbamate 80344-24-7 89581-82-8 149634-41-3 781675-84-1 781675-85-2 781675-86-3

ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation of thiadiazoline derivs. as M-stage kinesin inhibitors)

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ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of thiadiazoline derivs. as M-stage kinesin inhibitors)

INDEX TERM: 546112-13-4P 546112-14-5P 546112-15-6P 546112-16-7P
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ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of thiadiazoline derivs. as M-stage kinesin inhibitors)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD.

REFERENCE(S):
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(3) Fisons Plc; JP 62-53976 A 1987 HCAPLUS
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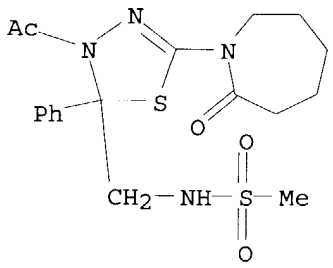
(6) Tao, E; US 4338449 A 1982 HCAPLUS

IT **546111-77-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of thiadiazoline derivs. as M-stage kinesin inhibitors)

RN 546111-77-7 HCAPLUS

CN 1,3,4-Thiadiazole-2-methanamine, 3-acetyl-5-(hexahydro-2-oxo-1H-azepin-1-yl)-2,3-dihydro-N-(methylsulfonyl)-2-phenyl- (9CI) (CA INDEX NAME)



L52 ANSWER 6 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:696379 HCAPLUS

DOCUMENT NUMBER: 141:225529

ENTRY DATE: Entered STN: 26 Aug 2004

TITLE: Preparation of hexahydropyrazino[1,2-a]pyrimidine-4,7-diones as anorectic agents.

INVENTOR(S): Flohr, Stefanie; Stengelin, Siegfried; Gossel, Matthias; Klabunde, Thomas; Stahl, Petra; Safar, Pavel; Spoonamore, James; Smrcina, Martin; Klein,

Joseph T.; Merriman, Gregory H.; Whiteley, Brian K.; Lanter, Carolina; Bordeau, Kenneth J.; Yang, Zhaoxia

PATENT ASSIGNEE(S): Aventis Pharma Deutshland GmbH, Germany
SOURCE: PCT Int. Appl., 270 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: German
INT. PATENT CLASSIF.:
MAIN: C07D487-04
SECONDARY: A61K031-519; A61P003-04; C07D241-00; C07D239-00
CLASSIFICATION: 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 34

FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004072077	A1	20040826	WO 2004-EP770		20040129
W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI					
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DE 10305885	A1	20040826	DE 2003-10305885		20030213
PRIORITY APPLN. INFO.:			DE 2003-10305885	A	20030213
			DE 2003-10349671	A	20031024

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004072077	ICM	C07D487-04
	ICS	A61K031-519; A61P003-04; C07D241-00; C07D239-00

OTHER SOURCE(S): MARPAT 141:225529
GRAPHIC IMAGE:

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

ABSTRACT:
Title compds. I [Z = (CH2)m-A; A = 3-12 membered mono, bi, or spirobicyclic ring; m = 0-6; Y = (CH2)n; n = 0-1; R1 = alkanyl, alkenyl, alkynyl, etc.; R2 = H, halo, OH, etc.; R3, R4, R5 = H, halo, OH, etc.] and their pharmaceutically acceptable salts were prepared For example, sodium cyanoborohydride mediated reductive amination of amine II, e.g., prepared via the sequential peptide coupling of isopropylamine, Fmoc-(S)-4-chlorophenylalanine, Z-Dap(Fmoc) and 2-methoxy-5-chlorobenzenesulfonyl chloride on bromoacetal-linker resin, followed by formic acid cleavage-condensation-cyclization, with acetaldehyde afforded pyrazinopyrimidine III. Compds. I are claimed useful for the treatment of anorexia.

SUPPL. TERM: hexahydropyrazinopyrimidinyldione prepn solid phase

synthesis; antianorexia agent hexahydropyrazinopyrimidinyldi one prepn

INDEX TERM: Drugs
(appetite stimulants, medicaments with; preparation of pyrazinopyrimidinyldiones as anorectic agents.)

INDEX TERM: Sexual behavior
(disorder, treatment of; preparation of pyrazinopyrimidinyldiones as anorectic agents.)

INDEX TERM: Combination chemotherapy
(medicaments with; preparation of pyrazinopyrimidinyldiones as anorectic agents.)

INDEX TERM: Disease, animal
(metabolic syndrome X, treatment of; preparation of pyrazinopyrimidinyldiones as anorectic agents.)

INDEX TERM: Diabetes mellitus
(non-insulin-dependent, treatment of; preparation of pyrazinopyrimidinyldiones as anorectic agents.)

INDEX TERM: Human
Solid phase synthesis
(preparation of pyrazinopyrimidinyldiones as anorectic agents.)

INDEX TERM: Appetite
(stimulants, medicaments with; preparation of pyrazinopyrimidinyldiones as anorectic agents.)

INDEX TERM: Anorexia
Antidiabetic agents
Antiobesity agents
Cachexia
Obesity
(treatment of; preparation of pyrazinopyrimidinyldiones as anorectic agents.)

INDEX TERM: 9028-35-7
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(medicaments with; preparation of pyrazinopyrimidinyldiones as anorectic agents.)

INDEX TERM: 746671-85-2P 746671-87-4P 746672-05-9P 748160-40-9P
ROLE: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of pyrazinopyrimidinyldiones as anorectic agents.)

INDEX TERM: 746671-90-9P 746671-91-0P 746671-92-1P 746671-93-2P
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748162-34-7P 748162-35-8P 748162-36-9P 748162-37-0P
ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrazinopyrimidinyldiones as anorectic agents.)

INDEX TERM:

748162-38-1P 748162-39-2P 748162-40-5P 748162-41-6P
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ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrazinopyrimidinyldiones as anorectic agents.)

INDEX TERM: 50-00-0, Formaldehyde, reactions 55-86-7 67-64-1, Acetone, reactions 75-07-0, Acetaldehyde, reactions 75-31-0, Isopropylamine, reactions 76-05-1, reactions 78-84-2, Isobutyraldehyde 98-09-9, Benzenesulfonyl chloride 98-98-6, 2-Pyridinecarboxylic acid 107-11-9, Allylamine 108-24-7, Acetic acid anhydride 108-94-1, Cyclohexanone, reactions 109-64-8, 1,3-Dibromopropane 109-90-0, Ethylisocyanate 110-52-1, 1,4-Dibromobutane 110-91-8, Morpholine, reactions 111-24-0, 1,5-Dibromopentane 121-44-8, Triethylamine, reactions 124-63-0, Methanesulfonyl chloride 407-25-0, Trifluoroacetic acid anhydride 452-83-5 501-53-1, Benzylchloroformate 501-81-5, 3-Pyridylacetic acid 619-84-1, 4-Dimethylaminobenzoic acid 645-36-3, 1-Amino-2,2-diethoxyethane 696-59-3, 2,5-Dimethoxytetrahydrofuran 701-27-9, 3-Fluorobenzenesulfonyl chloride 762-49-2, 1-Bromo-2-fluoroethane 765-30-0, Cyclopropylamine 1483-28-9, 2,5-Dimethoxybenzenesulfonyl chloride 1489-69-6, Cyclopropanecarboxaldehyde 1575-61-7, 5-Chloropentanoyl chloride 1609-86-5, tert-Butylisocyanate 1759-53-1, Cyclopropanecarboxylic acid 2032-35-1 2516-34-9, Cyclobutylamine 2564-95-6 2719-27-9, Cyclohexanecarbonyl chloride 2905-21-7, 2-Fluorobenzenesulfonyl chloride 2937-50-0, Allyl chloroformate 3612-20-2, 1-Benzyl-4-piperidone 4023-34-1, Cyclopropanecarbonyl chloride 4524-93-0, Cyclopentanecarbonyl chloride 4635-59-0, 4-Chlorobutyryl chloride 4755-50-4, 4-Dimethylaminobenzoyl chloride 5006-22-4, Cyclobutanecarbonyl chloride 5402-73-3, 2,5-Dichlorobenzenesulfonyl chloride 5414-19-7, 2-Bromoethyl ether 5424-29-3 5521-55-1 6480-68-8, 3-Quinolinecarboxylic acid 7424-00-2, 4-Chlorophenylalanine 7446-09-5, Sulfurdioxide, reactions 10314-99-5 13918-92-8, 2,4-Difluorobenzenesulfonyl chloride 16271-33-3, 2,4-Dichlorobenzenesulfonyl chloride 18635-43-3 19347-73-0, 6-Chlorohexanoyl chloride 19847-10-0, Pyrazinecarbonyl chloride 20260-53-1, Nicotinoyl chloride, hydrochloride 22952-32-5 32133-35-0 32315-10-9, Triphosgene 67475-56-3 69128-20-7 69695-61-0, 2-Chloro-4-trifluoromethoxyaniline 71985-80-3, 1-Methylpiperidine-4-carboxylic acid, hydrochloride 103321-52-4 105751-19-7 139631-62-2, Cyclopropanesulfonyl chloride 145758-05-0, 3,4-Difluorobenzenesulfonyl chloride 158063-66-2 175453-08-4 193693-64-0 250740-51-3 250740-52-4 253348-93-5 264276-42-8 276262-70-5 358780-13-9 376595-03-8 678991-30-5 678991-65-6 746672-87-7 746672-88-8 748162-98-3 748163-22-6 748163-99-7 748164-00-3
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation of pyrazinopyrimidinyldiones as anorectic agents.)

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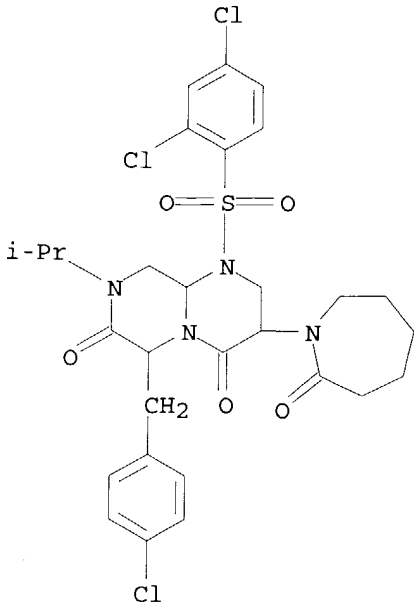
748164-65-0P 748164-66-1P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of pyrazinopyrimidinyldiones as anorectic agents.)

IT **748160-66-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrazinopyrimidinyldiones as anorectic agents.)

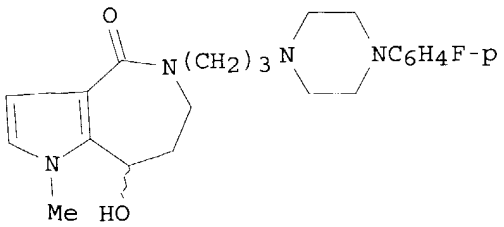
RN 748160-66-9 HCAPLUS
CN 2H-Pyrazino[1,2-a]pyrimidine-4,7(3H,6H)-dione, 6-[(4-chlorophenyl)methyl]-

1-[(2,4-dichlorophenyl)sulfonyl]-3-(hexahydro-2-oxo-1H-azepin-1-yl)tetrahydro-8-(1-methylethyl)- (9CI) (CA INDEX NAME)



L52 ANSWER 7 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	2000:311250 HCAPLUS
DOCUMENT NUMBER:	133:104983
ENTRY DATE:	Entered STN: 14 May 2000
TITLE:	Synthesis and serotonin 2 (5-HT2) receptor antagonist activity of 5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and related compounds
AUTHOR(S):	Mizuno, Akira; Ogata, Atsuto; Kamei, Tomoe; Shibata, Makoto; Shimamoto, Tetsuo; Hayashi, Yasuhiro; Nakanishi, Kyoko; Takiguchi, Chikako; Oka, Naomi; Inomata, Norio
CORPORATE SOURCE:	Suntory Institute for Biomedical Research, Osaka, 618-8503, Japan
SOURCE:	Chemical & Pharmaceutical Bulletin (2000), 48(5), 623-635 CODEN: CPBTAL; ISSN: 0009-2363
PUBLISHER:	Pharmaceutical Society of Japan
DOCUMENT TYPE:	Journal
LANGUAGE:	English
CLASSIFICATION:	28-2 (Heterocyclic Compounds (More Than One Hetero Atom)) Section cross-reference(s): 1
OTHER SOURCE(S):	CASREACT 133:104983
GRAPHIC IMAGE:	



I

ABSTRACT:
A series of 5-aminoalkylpyrrolo[3,2-c]azepine derivs. was synthesized and their serotonin 2 (5-HT2) receptor antagonist and antiplatelet aggregation activities were evaluated. 5-HT2 receptor antagonist activity was largely determined by the nature of the substituent at the 8-position as well as the aminoalkyl group at the 5-position of the pyrrolo[3,2-c]azepine ring. Compound I was recognized as having potent 5-HT2 receptor antagonist activity with weak α1 adrenoceptor blocking activity and no significant D2 receptor binding affinity. (±)-I was resolved directly via diastereomeric salt formation and each enantiomer was evaluated. The 5-HT2 receptor antagonist activity of I was found to reside primarily in (-)-I (α-OH) (which was about 14-fold more potent than (+)-I (β-OH) in isolated guinea pig arteries). Consequently, (S)-(-)-I (SUN C5174) displayed the overall best profile with potent 5-HT2 receptor antagonist activity (pA2=8.98±0.06) and high selectivity vs. other receptors. SUN C5174 showed a marked inhibitory effect on the platelet aggregation induced by serotonin in combination with collagen and ADP in canine or human platelet-rich plasma (IC50=6.5 to 16 nM). SUN C5174 significantly inhibited the mortality rate in mouse acute pulmonary thromboembolitic death induced by collagen and serotonin at oral doses of 0.3 mg/kg or higher. SUN C5174 is currently undergoing clin. evaluation.

SUPPL. TERM: pyrroloazepine prepn serotonin 5HT2 receptor antagonist; serotonin induced platelet aggregation inhibition pyrroloazepine SUN C5174

INDEX TERM: 5-HT antagonists
(5-HT2A; preparation and serotonin 2 (5-HT2) receptor antagonist activity of 5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and related compds.)

INDEX TERM: Crystal structure
Molecular structure
(of fluorophenylpiperazinylpropyl pyrrolo[3,2-c]azepinoone derivative)

INDEX TERM: Structure-activity relationship
(platelet aggregation-inhibiting; preparation and serotonin 2 (5-HT2) receptor antagonist activity of 5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and related compds.)

INDEX TERM: Heterocyclization
Platelet aggregation inhibitors
(preparation and serotonin 2 (5-HT2) receptor antagonist activity of 5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and related compds.)

INDEX TERM: Structure-activity relationship
(receptor-inhibiting; preparation and serotonin 2 (5-HT2) receptor antagonist activity of 5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and related compds.)

INDEX TERM: 282550-44-1P
ROLE: PRP (Properties); SPN (Synthetic preparation); PREP

(Preparation)
(crystal structure; preparation and serotonin 2 (5-HT2) receptor antagonist activity of 5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and related compds.)

INDEX TERM: 191592-02-6P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(nod *preparation and serotonin 2 (5-HT2) receptor antagonist activity of 5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and related compds.)

INDEX TERM: 74050-98-9, Ketanserin 125926-17-2, Sarpogrelate 135963-42-7
ROLE: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(preparation and serotonin 2 (5-HT2) receptor antagonist activity of 5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and related compds.)

INDEX TERM: 191591-86-3P 191591-92-1P 191592-08-2P 191592-09-3P 191592-10-6P 191592-12-8P 191592-13-9P 191592-14-0P 191592-16-2P 191592-17-3P 191592-18-4P 191592-19-5P 191592-20-8P 191592-21-9P 191592-22-0P 191592-23-1P 191592-24-2P 191592-25-3P 191592-27-5P 191592-30-0P 282550-43-0P
ROLE: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation and serotonin 2 (5-HT2) receptor antagonist activity of 5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and related compds.)

INDEX TERM: 191592-15-1P 191592-35-5P 191592-36-6P **282550-35-0P** 282550-39-4P
ROLE: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and serotonin 2 (5-HT2) receptor antagonist activity of 5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and related compds.)

INDEX TERM: 282550-33-8P
ROLE: BYP (Byproduct); PREP (Preparation)
(preparation and serotonin 2 (5-HT2) receptor antagonist activity of 5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and related compds.)

INDEX TERM: 75-03-6, Iodoethane 87-69-4, L-(+)-Tartaric acid, reactions 109-70-6, 1-Bromo-3-chloropropane 140-88-5, Ethyl acrylate 147-71-7, D-(-)-Tartaric acid 931-03-3, 1H-Pyrrole-3-carboxylic acid 2252-63-3, 1-(4-Fluorophenyl)piperazine 2703-17-5, Methyl pyrrole-3-carboxylate 6276-54-6, 3-Chloropropylamine hydrochloride 25519-78-2, 4-(4-Fluorobenzoyl)piperidine hydrochloride 27019-47-2, β-Alanine benzyl ester p-toluenesulfonate 99972-42-6
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation and serotonin 2 (5-HT2) receptor antagonist activity of 5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and related compds.)

INDEX TERM: 36929-61-0P 40611-74-3P, Methyl 1-methyl-1H-pyrrole-3-carboxylate 155177-46-1P 191591-53-4P 191591-55-6P 191591-57-8P 191591-59-0P 191591-61-4P 191591-63-6P

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191591-77-2P 191591-80-7P 191591-81-8P 191591-82-9P
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191591-96-5P 191591-97-6P 191591-98-7P 191591-99-8P
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191592-38-8P 282550-40-7P 282550-41-8P 282550-42-9P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and serotonin 2 (5-HT2) receptor antagonist activity of 5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and related compds.)

INDEX TERM: 191591-62-5P 191591-65-8P 282550-34-9P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation and serotonin 2 (5-HT2) receptor antagonist activity of 5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and related compds.)

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD.

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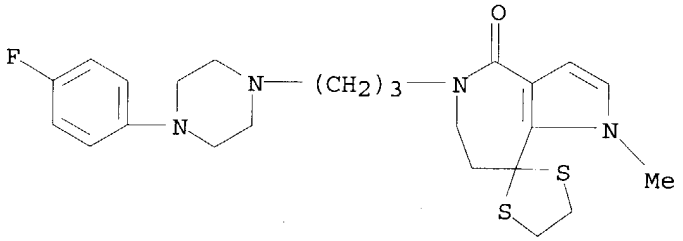
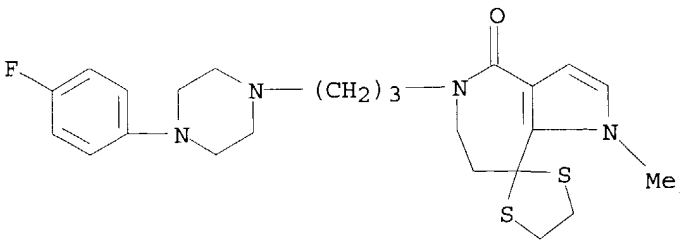
(48) Yamamura, H; Proc Natl Acad Sci USA 1974, V71, P1725 HCAPLUS
(49) Yevich, J; J Med Chem 1986, V29, P359 HCAPLUS

IT **282550-35-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and serotonin 2 (5-HT2) receptor antagonist activity of 5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and related compds.)
RN 282550-35-0 HCAPLUS
CN Spiro[1,3-dithiolane-2,8'(1'H)-pyrrolo[3,2-c]azepin]-4'(5'H)-one, 5'-[3-[4-(4-fluorophenyl)-1-piperazinyl]propyl]-6',7'-dihydro-1'-methyl-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

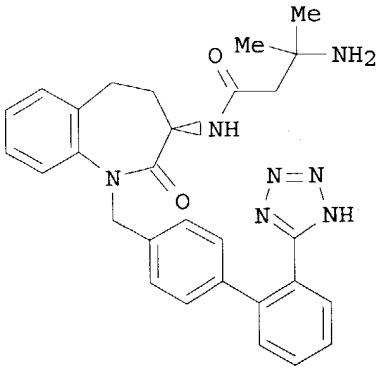
IT **191592-05-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and serotonin 2 (5-HT2) receptor antagonist activity of 5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and related compds.)
RN 191592-05-9 HCAPLUS
CN Spiro[1,3-dithiolane-2,8'(1'H)-pyrrolo[3,2-c]azepin]-4'(5'H)-one, 5'-[3-[4-(4-fluorophenyl)-1-piperazinyl]propyl]-6',7'-dihydro-1'-methyl- (9CI) (CA INDEX NAME)



L52 ANSWER 8 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:49724 HCAPLUS
DOCUMENT NUMBER: 126:171471
ENTRY DATE: Entered STN: 23 Jan 1997
TITLE: Benzolactam growth hormone secretagogues: replacement of the C-3 amide bond in L-692,429
AUTHOR(S): Ok, Hyun O.; Szumiloski, John L.; Doldouras, George A.; Schoen, William R.; Cheng, Kang; Chan, Wanda W.-S.; Butler, Bridget S.; Smith, Roy G.; Fisher, Michael H.; Wyvratt, Matthew J.
CORPORATE SOURCE: Departments Medicinal Chemistry Biochemistry Physiology, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1996), 6(24), 3051-3056
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 25

GRAPHIC IMAGE:



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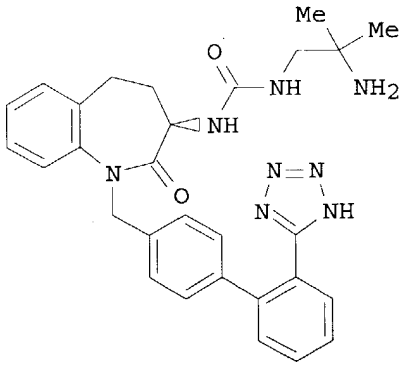

II

ABSTRACT:
The synthesis and structure-activity relationships of various C-3 amide bond modifications in the novel non-peptidyl growth hormone secretagogue L-692,429 (I) were described. An example derivative was II. Several C-3 amide surrogates were prepared and the urea moiety was found to exhibit growth hormone releasing activity similar to that observed with L-692,429.

SUPPL. TERM: growth hormone L 692429 deriv prepn; structure activity growth hormone L 692429; benzolactam prepn growth hormone L 692429

INDEX TERM: Structure-activity relationship
(preparation of L-692429 analogs as growth hormone secretagogues)

INDEX TERM: 145455-23-8DP, L-692429, analogs
ROLE: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(Benzolactam growth hormone secretagogues: replacement of the C-3 amide bond in L-692,429)

INDEX TERM: 9034-39-3, Growth hormone releasing factor 145456-63-9 187107-71-7
ROLE: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of L-692429 analogs as growth hormone secretagogues)

INDEX TERM: 140700-64-7P 145455-29-4P 145455-36-3P 145456-61-7P
156197-47-6P 169953-04-2P 169953-34-8P 169954-56-7P
187107-70-6P **187107-72-8P 187107-73-9P**
187107-74-0P 187107-75-1P
ROLE: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of L-692429 analogs as growth hormone secretagogues)

INDEX TERM: 124-68-5 42514-50-1 81445-44-5 81445-45-6
124750-51-2 137036-55-6 169954-70-5 187107-78-4
187107-79-5 187107-80-8 187107-81-9
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation of L-692429 analogs as growth hormone secretagogues)

INDEX TERM: 109608-77-7P 145485-84-3P 145485-87-6P 181646-38-8P
187107-76-2P 187107-77-3P 187107-82-0P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of L-692429 analogs as growth hormone secretagogues)

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD.

REFERENCE(S):

(1) Armstrong, J; Tetrahedron Lett 1994, V35, P3239 HCAPLUS
(2) Bowers, C; J Pedatr Endocrinol 1993, V6, P21 MEDLINE
(3) Devita, R; Drugs of the Future 1996, V21, P273 HCAPLUS
(4) Gertz, B; J Clin Endocrinol Metab 1993, V77, P1393 HCAPLUS
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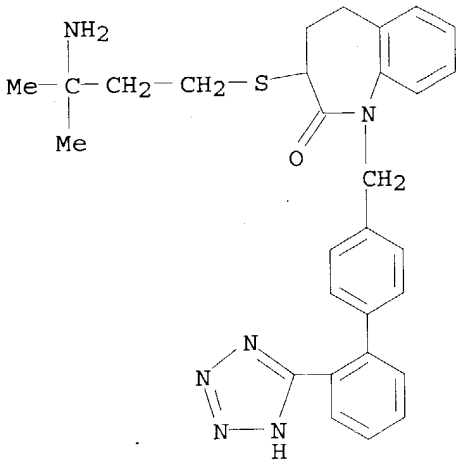
(7) Ok, D; Bioorg Med Chem Lett 1994, V4, P2709 HCAPLUS
(8) Schoen, W; Annual Reports in Medicinal Chemistry, Chapter 19 1993, V28 HCAPLUS
(9) Schoen, W; J Med Chem 1994, V37, P897 HCAPLUS
(10) Smith, R; Science 1993, V260, P1640 HCAPLUS
(11) Strobl, J; Pharmacological Reviews 1994, V46, P1 HCAPLUS
(12) Thorner, M; Acta Paediatr Suppl 1993, V388, P2 MEDLINE

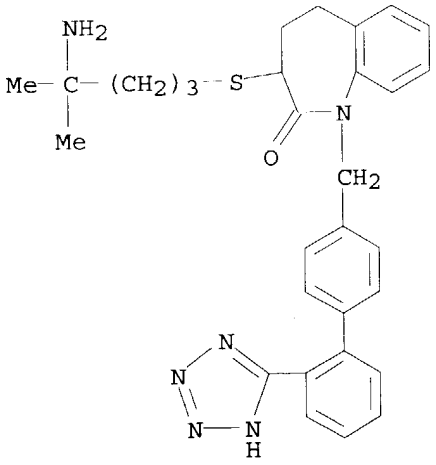
IT **187107-72-8P 187107-73-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological

study); PREP (Preparation)
(preparation of L-692429 analogs as growth hormone secretagogues)

RN 187107-72-8 HCAPLUS
CN 2H-1-Benzazepin-2-one, 3-[(3-amino-3-methylbutyl)thio]-1,3,4,5-tetrahydro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



RN 187107-73-9 HCAPLUS
CN 2H-1-Benzazepin-2-one, 3-[(4-amino-4-methylpentyl)thio]-1,3,4,5-tetrahydro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L52 ANSWER 9 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	1995:902676 HCAPLUS
DOCUMENT NUMBER:	123:313795
ENTRY DATE:	Entered STN: 08 Nov 1995
TITLE:	Preparation of ureidobenzaepinones as growth hormone release stimulants
INVENTOR(S):	Ok, Hyun O.; Schoen, William R.; Szumiloski, John
PATENT ASSIGNEE(S):	Merck and Co., Inc., USA
SOURCE:	PCT Int. Appl., 145 pp.

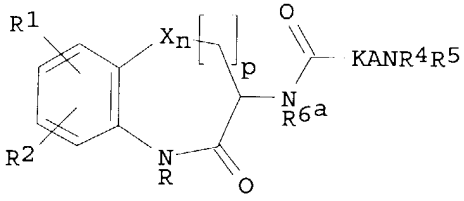
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.:
MAIN: C07D223-16
SECONDARY: C07D261-10; A61K031-55
CLASSIFICATION: 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9516675	A1	19950622	WO 1994-US14374	19941209
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9513718	A1	19950703	AU 1995-13718	19941209
PRIORITY APPLN. INFO.:			US 1993-149482	19931213
			WO 1994-US14374	19941209

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9516675	ICM	C07D223-16
	ICS	C07D261-10; A61K031-55

OTHER SOURCE(S): MARPAT 123:313795
GRAPHIC IMAGE:



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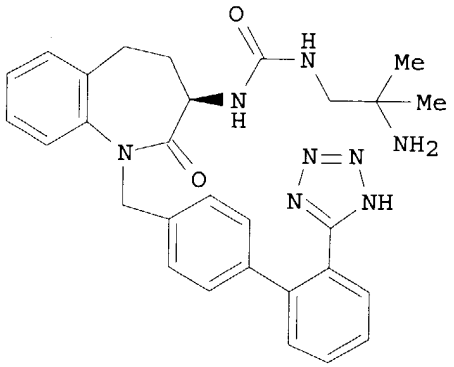

II

ABSTRACT:
Title compds. [I; A = (1h)xCR8aR8b(CH2)y; K = O, S, NR6b; R = (CH2)qLwR3; L = (un)substituted phenylene; R1,R2 = H, halo, (perfluoro)alkyl, etc.; R3 =

(un)substituted Ph; R4,R5,R8a,R8b = H, alkyl, (un)substituted Ph, etc.; NR4R5 = heterocyclyl; R6a,R6b = H, (phenyl)alkyl, Ph, etc.; X = CO, O, SO0-2, CH(OH), NH, CH:CH, etc.; n,w = 0 or 1; p,x,y, = 0-3; q = 0-4] were prepared as growth hormone release stimulants (no data). Thus, H2NCH2CMe2NHCO2CMe3 (preparation given) was treated with COCl2 and the product condensed with 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one to give the urea which was N-alkylated with N-triphenylmethyl-5-(4'-bromomethyl-2-biphenylyl)tetrazole to give, after deprotection, title compound II.

SUPPL. TERM: ureidobenzaepinone prepn growth hormone release stimulant

INDEX TERM:

169953-04-2P	169953-05-3P	**169953-06-4P**	
169953-07-5P	169953-08-6P	169953-09-7P	169953-10-0P
169953-11-1P	169953-12-2P	169953-13-3P	
169953-14-4P	169953-15-5P	169953-16-6P	169953-17-7P
169953-18-8P	169953-19-9P	**169953-20-2P**	
169953-21-3P	169953-22-4P	169953-23-5P	169953-24-6P
169953-25-7P	169953-26-8P	169953-27-9P	
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169953-32-6P	**169953-33-7P**	169953-34-8P	
169953-35-9P	**169953-36-0P**	169953-37-1P	
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169953-48-4P	169953-49-5P	**169953-50-8P**	
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169953-92-8P	**169953-93-9P**	169953-94-0P	
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169954-07-8P	169954-08-9P	169954-09-0P	169954-10-3P
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169954-15-8P	169954-16-9P	169954-17-0P	169954-18-1P
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169954-62-5P	169954-64-7P	169954-66-9P	

ROLE: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of ureidobenzaepinones as growth hormone release stimulants)

INDEX TERM: 9002-72-6, Growth hormone
ROLE: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of ureidobenzaepinones as growth hormone release stimulants)

INDEX TERM: 110-87-2 501-53-1, Benzyl chloroformate 577-19-5, 2-Bromonitrobenzene 811-93-8, 1,2-Diamino-2-methylpropane 5720-05-8, 4-Tolylboronic acid 7699-00-5, Ethyl D-lactate 24424-99-5, Di-tert-butyl dicarbonate 30674-80-7 81445-44-5, (S)-2-Benzyloxypropanal 124750-51-2 169954-84-1
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation of ureidobenzaepinones as growth hormone release stimulants)

INDEX TERM: 70680-21-6P 81445-45-6P, (R)-2-Benzyloxypropanal 114772-39-3P 156892-82-9P 159815-76-6P 159815-77-7P 159815-78-8P 169188-17-4P 169954-67-0P 169954-68-1P 169954-69-2P 169954-70-5P 169954-71-6P 169954-73-8P 169954-74-9P 169954-75-0P 169954-76-1P 169954-77-2P 169954-78-3P 169954-79-4P 169954-80-7P 169954-82-9P 169954-83-0P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of ureidobenzaepinones as growth hormone release stimulants)

IT **169953-06-4P 169953-11-1P 169953-18-8P**
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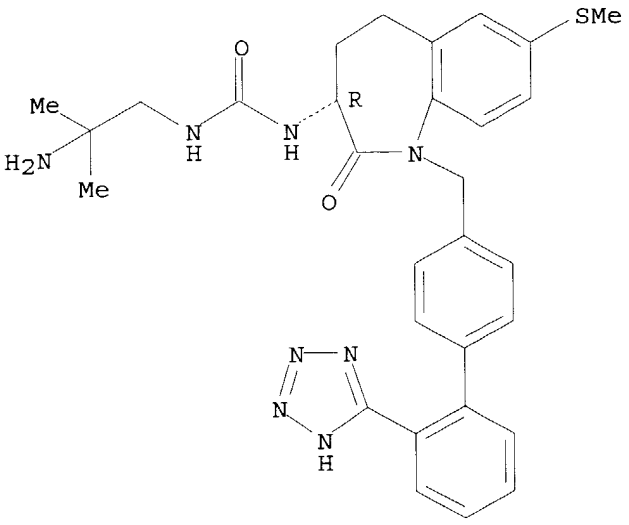
169953-36-0P 169953-41-7P 169953-48-4P
169953-50-8P 169953-55-3P 169953-63-3P
169953-66-6P 169953-71-3P 169953-78-0P
169953-80-4P 169953-85-9P 169953-93-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of ureidobenzaepinones as growth hormone release stimulants)

RN 169953-06-4 HCAPLUS

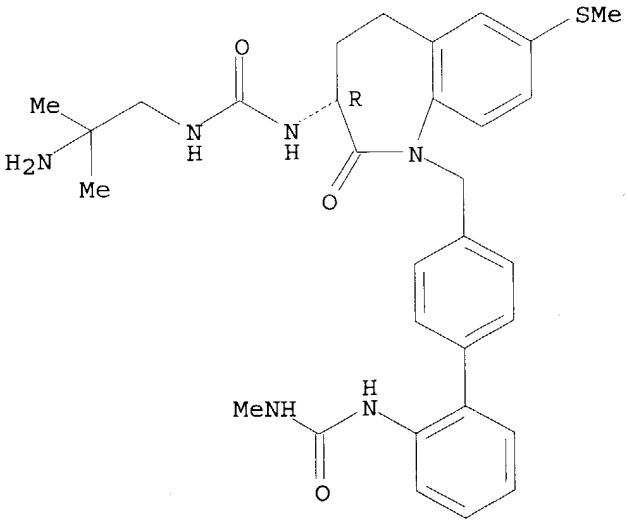
CN Urea, N-(2-amino-2-methylpropyl)-N'-[2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



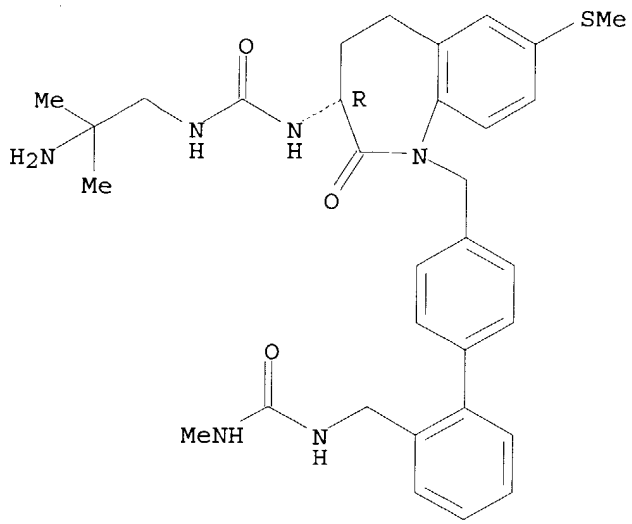
RN 169953-11-1 HCAPLUS
CN Urea, N-[4'-[[3-[[[(2-amino-2-methylpropyl)amino]carbonyl]amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-yl]-N'-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



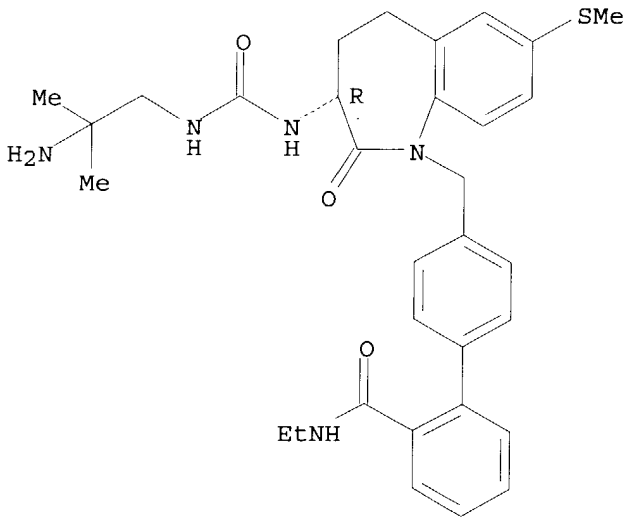
RN 169953-18-8 HCAPLUS
CN Urea, N-[[4'-[[3-[[[(2-amino-2-methylpropyl)amino]carbonyl]amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-yl]methyl]-N'-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



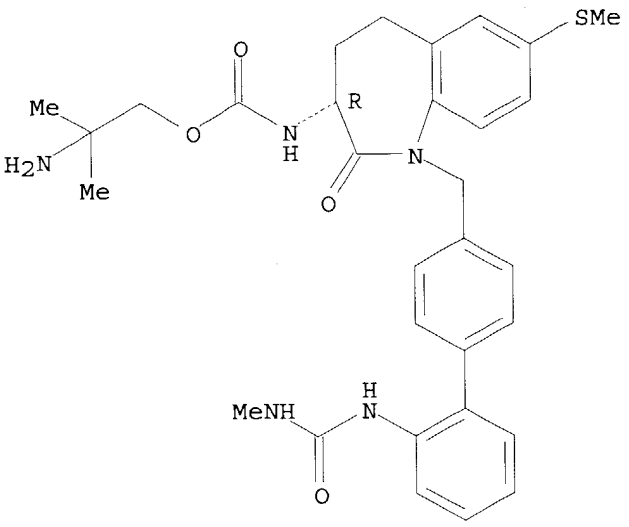
RN 169953-20-2 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxamide, 4'-[[3-[[[(2-amino-2-methylpropyl)amino]carbonyl]amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl]-N-ethyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



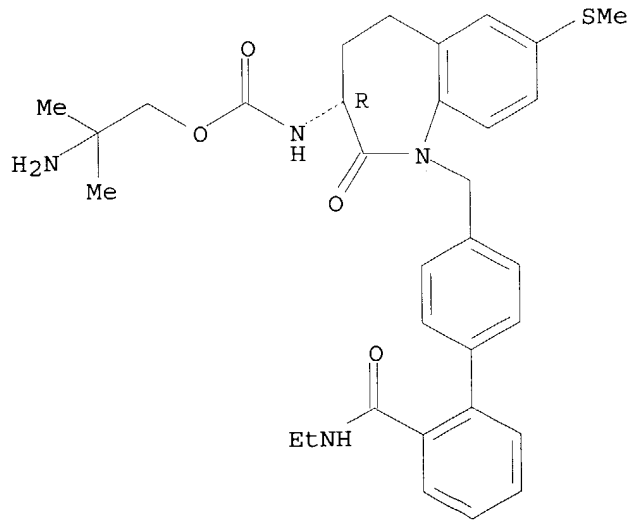
RN 169953-25-7 HCAPLUS
CN Carbamic acid, [2,3,4,5-tetrahydro-1-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, 2-amino-2-methylpropyl ester, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



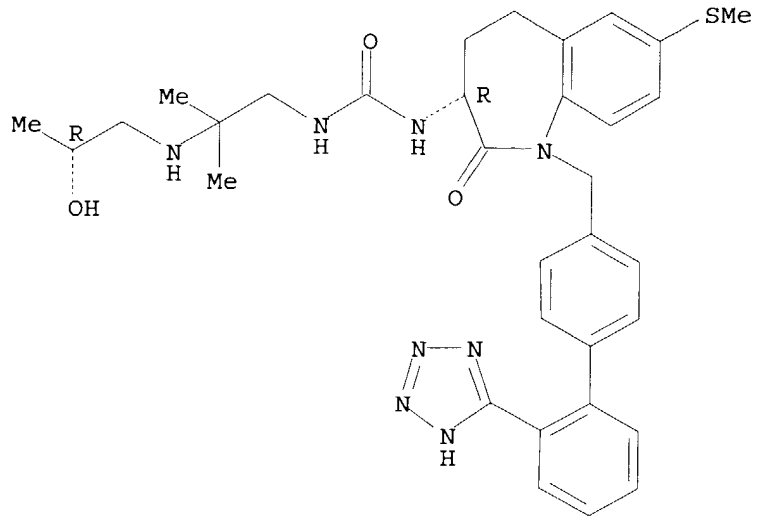
RN 169953-33-7 HCAPLUS
CN Carbamic acid, [1-[[2'-[(ethylamino)carbonyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, 2-amino-2-methylpropyl ester, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



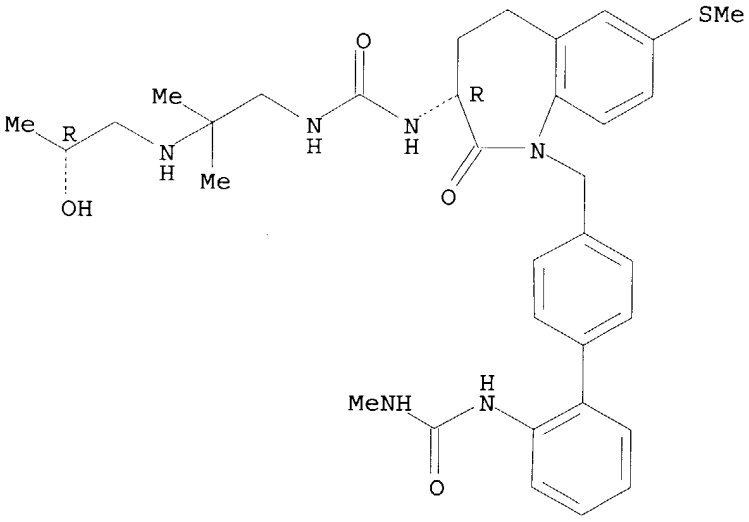
RN 169953-36-0 HCAPLUS
CN Urea, N-[2-[(2-hydroxypropyl)amino]-2-methylpropyl]-N'-[2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



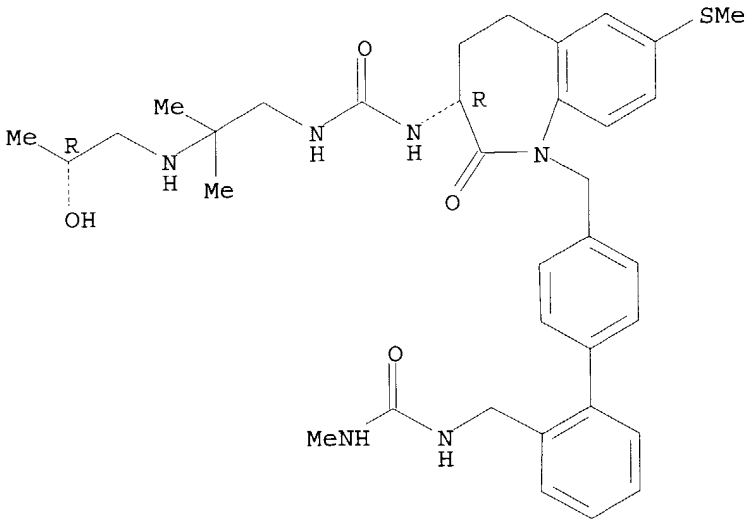
RN 169953-41-7 HCAPLUS
CN Urea, N-[2-[(2-hydroxypropyl)amino]-2-methylpropyl]-N'-[2,3,4,5-tetrahydro-1-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



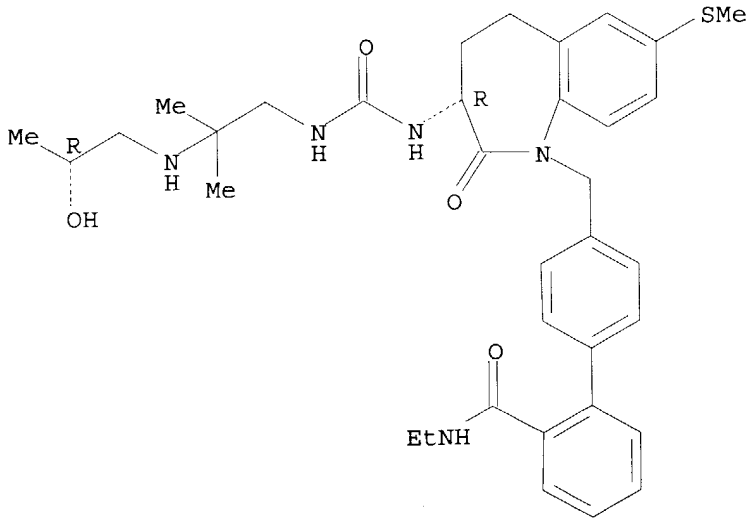
RN 169953-48-4 HCAPLUS
CN Urea, N-[2-[(2-hydroxypropyl)amino]-2-methylpropyl]-N'-[2,3,4,5-tetrahydro-1-[[2'-[[[(methylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



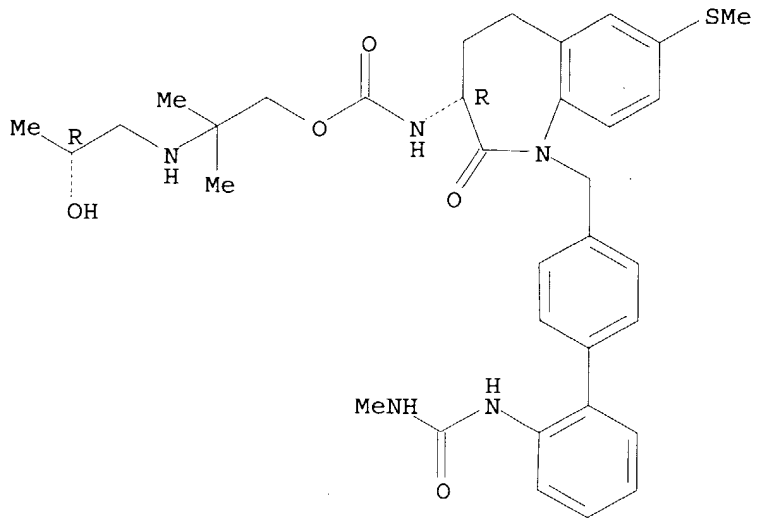
RN 169953-50-8 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxamide, N-ethyl-4'-[[2,3,4,5-tetrahydro-3-[[[[2-[(2-hydroxypropyl)amino]-2-methylpropyl]amino]carbonyl]amino]-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



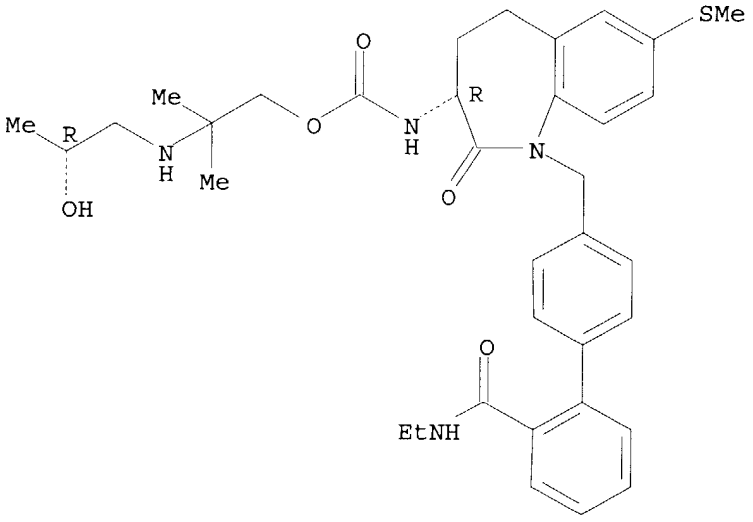
RN 169953-55-3 HCAPLUS
CN Carbamic acid, [2,3,4,5-tetrahydro-1-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, 2-[(2-hydroxypropyl)amino]-2-methylpropyl ester, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



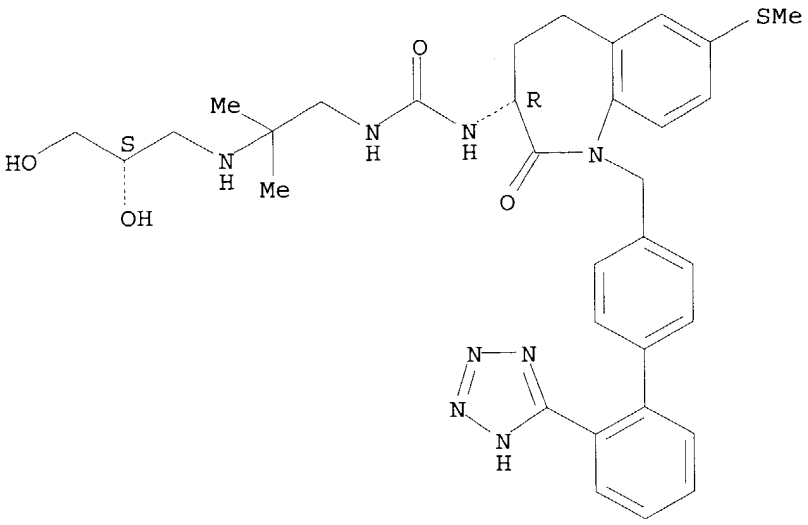
RN 169953-63-3 HCAPLUS
CN Carbamic acid, [1-[[2'-[(ethylamino)carbonyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, 2-[(2-hydroxypropyl)amino]-2-methylpropyl ester, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



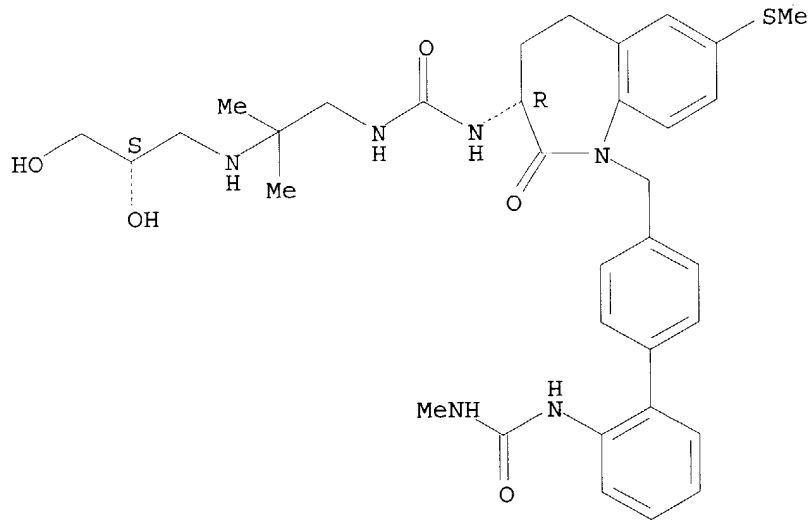
RN 169953-66-6 HCAPLUS
CN Urea, N-[2-[(2,3-dihydroxypropyl)amino]-2-methylpropyl]-N'-[2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



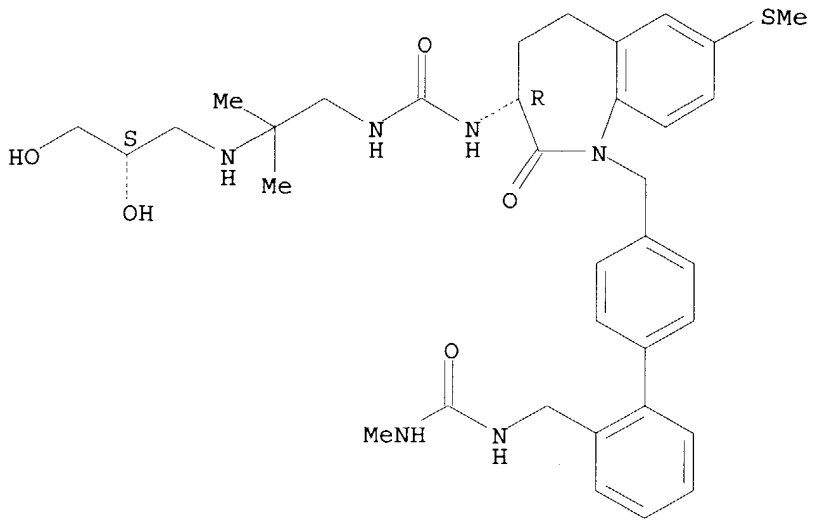
RN 169953-71-3 HCAPLUS
CN Urea, N-[4'-[[3-[[[[2-[(2,3-dihydroxypropyl)amino]-2-methylpropyl]amino]carbonyl]amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-yl]-N'-methyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



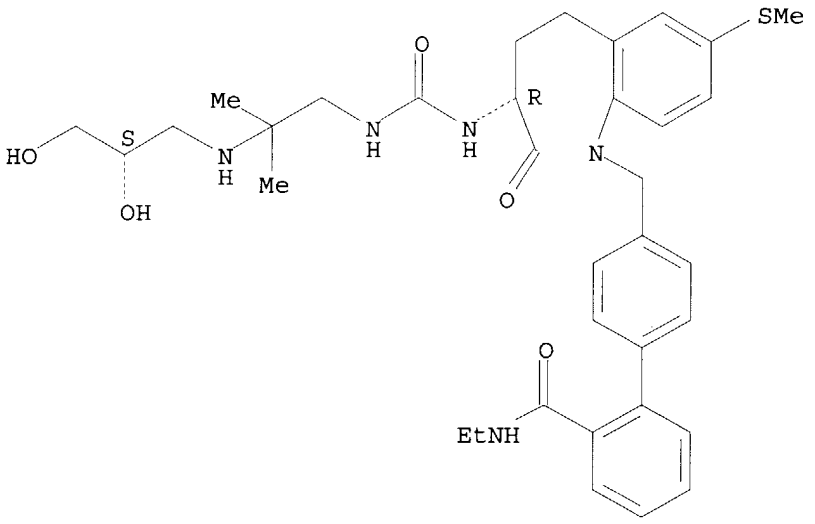
RN 169953-78-0 HCAPLUS
CN Urea, N-[[4'-[[3-[[[[2-[(2,3-dihydroxypropyl)amino]-2-methylpropyl]amino]carbonyl]amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-yl]methyl]-N'-methyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



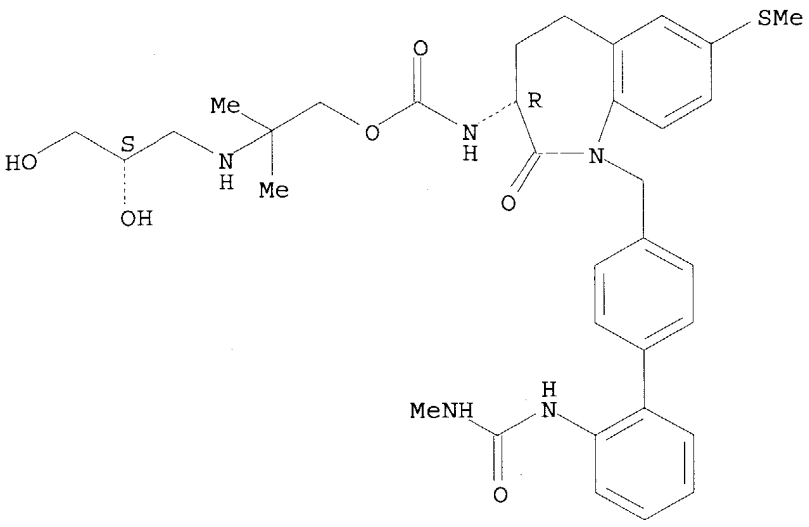
RN 169953-80-4 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxamide, 4'-[[3-[[[[2-[(2,3-dihydroxypropyl)amino]-2-methylpropyl]amino]carbonyl]amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl]-N-ethyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



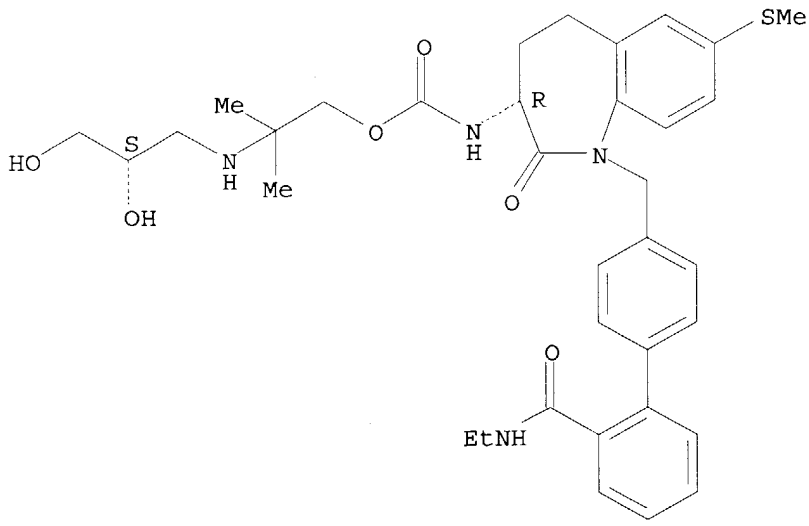
RN 169953-85-9 HCAPLUS
CN Carbamic acid, [2,3,4,5-tetrahydro-1-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, 2-[(2,3-dihydroxypropyl)amino]-2-methylpropyl ester, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 169953-93-9 HCAPLUS
CN Carbamic acid, [1-[[2'-[(ethylamino)carbonyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, 2-[(2,3-dihydroxypropyl)amino]-2-methylpropyl ester, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L52 ANSWER 10 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:807968 HCAPLUS
DOCUMENT NUMBER: 123:228011
ENTRY DATE: Entered STN: 23 Sep 1995
TITLE: Preparation of N-(benzazepinonyl)alkanamides as growth hormone release promoters
INVENTOR(S): Bochis, Richard J.; Hodges, Paul J.; Schoen, William R.; Wyvratt, Matthew J., Jr.

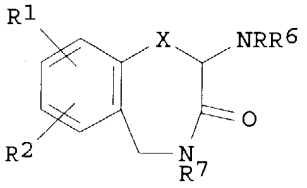
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 185 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.:
MAIN: A61K031-55
SECONDARY: C07D209-34; C07D215-227; C07D223-16
CLASSIFICATION: 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9509633	A1	19950413	WO 1994-US11086	19940930
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5545735	A	19960813	US 1993-132074	19931004
AU 9479616	A1	19950501	AU 1994-79616	19940930
PRIORITY APPLN. INFO.:			US 1993-132074 A	19931004
			WO 1994-US11086 W	19940930

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9509633	ICM	A61K031-55
	ICS	C07D209-34; C07D215-227; C07D223-16
US 5545735	ECLA	C07D201/10; C07D223/16C; C07D403/10; C07D417/10

OTHER SOURCE(S): MARPAT 123:228011
GRAPHIC IMAGE:



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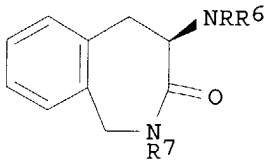

II

ABSTRACT:
Title compds. [I; R = COANR4R5; A = (CH2)xCR8R8a(CH2)y; R1,R2 = H, halo, (prefluoro)alkyl(oxy), etc.; R4,R5 = H, alk(en)yl, Ph, etc.; R6 = H, alkyl, phenyl(alkyl); R7 = (CH2)qLwR9; L = (un)substituted phenylene; R8,R8a = H, alkyl, CF3, Ph, etc.; R9 = (un)substituted Ph; X = CH2, SO0-2; q = 0-4; x,y = 0-3; w = 0 or 1] were prepared as growth hormone release promoters (no data). Thus, tert-Bu (2S,3R)-6-oxo-2,3-diphenylmorpholine-4-carboxylate was alkylated with 2-(NC)C6H4CH2Br and the product treated with NaBH4/Co(NO3)2 to give benzazepine II [R = (1R,2S)-(CHPh)2OH, R6 = CO2CMe3, R7 = H] which was N-alkylated with 4-(BrH2C)C6H4C6H4NO2-2 (preparation given) and the product converted in 3 steps to II [R7 = CH2C6H4[C6H4(NHCONHMe)-4]-4](III; R = R6 = H). The latter was amidated by Me3CO2CNHCMe2CH2CO2H to give, after deprotection, III (R7 = COCH2CMe2NH2).

SUPPL. TERM: benzazepinonylalkanamide prepn growth hormone release promoter

INDEX TERM: Antiobesity agents
(preparation of N-(benzazepinonyl)alkanamides as growth hormone release promoters)

INDEX TERM: Osteoporosis
(treatment; preparation of N-(benzazepinonyl)alkanamides as growth hormone release promoters)

INDEX TERM: Animal metabolism
(disorder, catabolic, nitrogen wasting; preparation of N-(benzazepinonyl)alkanamides as growth hormone release promoters)

INDEX TERM:

168056-97-1P	168057-00-9P	168057-01-0P	168057-02-1P
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168057-14-5P	**168057-15-6P**		
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ROLE: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of N-(benzazepinonyl)alkanamides as growth hormone release promoters)

INDEX TERM: 115-11-7, Isobutylene, reactions 577-19-5, 2-Bromonitrobenzene 873-75-6, 4-Bromobenzyl alcohol 3959-05-5, 2-Bromobenzylamine 5720-05-8, 4-Tolylboronic acid 22115-41-9, α-Bromo-o-toluonitrile 24424-99-5, Di-tert-butyl dicarbonate 30992-29-1, N-(tert-Butoxycarbonyl)-α-methylalanine 112741-50-1
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation of N-(benzazepinonyl)alkanamides as growth hormone release promoters)

INDEX TERM: 4879-95-2P, 4,4-Dimethylazetidin-2-one 70680-21-6P, 4-Methyl-2'-nitro-1,1'-biphenyl 114772-39-3P 129765-95-3P, 3-(tert-Butoxycarbonylamino)-3-methylbutanoic acid 133776-42-8P, 4-Bromobenzyl tert-butyldimethylsilyl ether 147239-62-1P 148289-82-1P 155300-46-2P 162356-90-3P, N-(tert-Butoxycarbonyl)-2-bromobenzylamine 162356-92-5P 162356-93-6P 168056-98-2P 168059-20-9P 168059-21-0P 168059-22-1P 168059-23-2P 168059-24-3P 168059-25-4P 168059-26-5P 168059-27-6P 168059-28-7P 168059-29-8P 168059-30-1P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of N-(benzazepinonyl)alkanamides as growth hormone release promoters)

INDEX TERM: 9002-72-6, Growth hormone
ROLE: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(release promoters; N-(benzazepinonyl)alkanamides)

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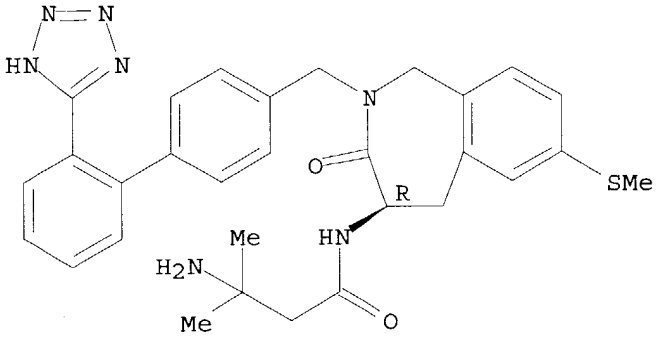
168057-16-7P 168057-25-8P 168057-26-9P
168057-27-0P 168057-37-2P 168057-45-2P
168057-46-3P 168057-47-4P 168057-55-4P
168057-61-2P 168057-67-8P 168057-69-0P
168057-72-5P 168057-78-1P 168057-84-9P
168057-88-3P 168057-92-9P 168057-96-3P
168058-00-2P 168058-04-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of N-(benzazepinonyl)alkanamides as growth hormone release promoters)

RN 168057-13-4 HCAPLUS

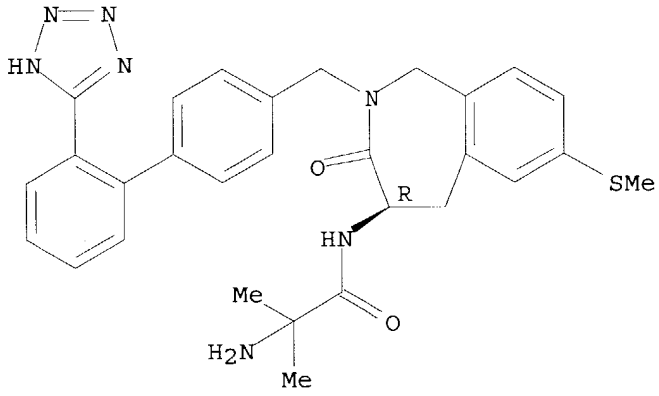
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-2-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



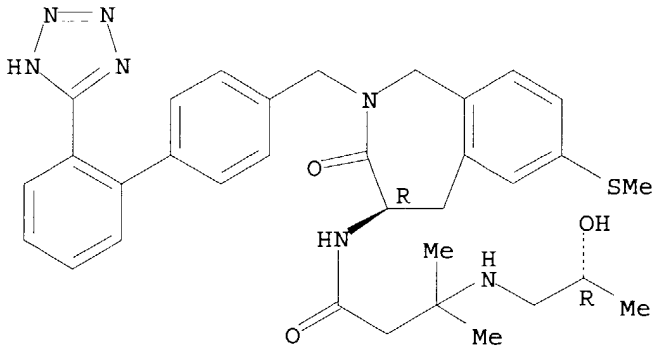
RN 168057-14-5 HCAPLUS
CN Propanamide, 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-2-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



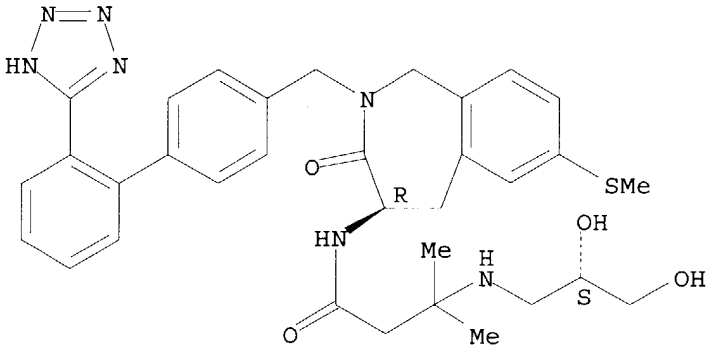
RN 168057-15-6 HCAPLUS
CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-2-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-2-benzazepin-4-yl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



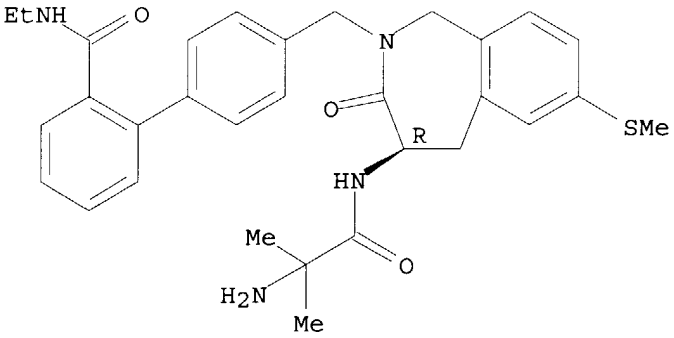
RN 168057-16-7 HCAPLUS
CN Butanamide, 3-[(2,3-dihydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-2-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-2-benzazepin-4-yl]-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 168057-25-8 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxamide, 4'-[[4-[(2-amino-2-methyl-1-oxopropyl)amino]-1,3,4,5-tetrahydro-7-(methylthio)-3-oxo-2H-2-benzazepin-2-yl]methyl]-N-ethyl-, (R)- (9CI) (CA INDEX NAME)

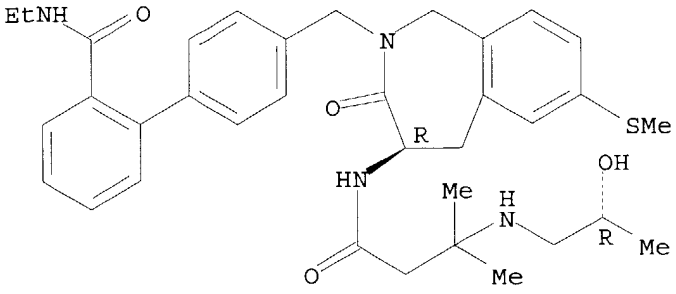
Absolute stereochemistry.



RN 168057-26-9 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxamide, N-ethyl-4'-[[1,3,4,5-tetrahydro-4-[[3-[(2-hydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-7-(methylthio)-3-oxo-2H-2-

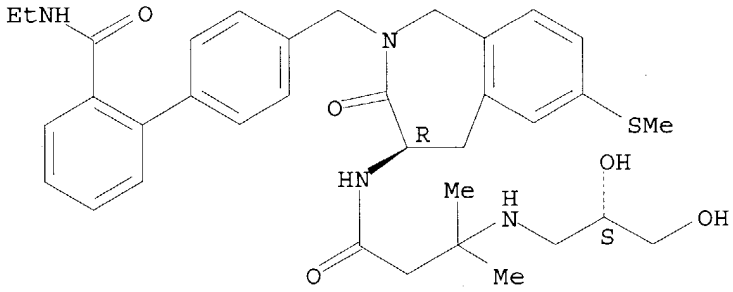
benzazepin-2-yl]methyl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



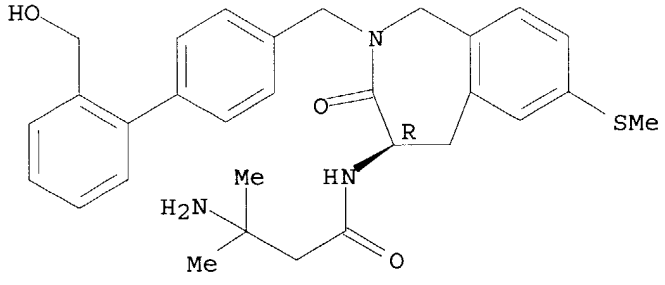
RN 168057-27-0 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxamide, 4'-[[4-[[3-[(2,3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-1,3,4,5-tetrahydro-7-(methylthio)-3-oxo-2H-2-benzazepin-2-yl]methyl]-N-ethyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



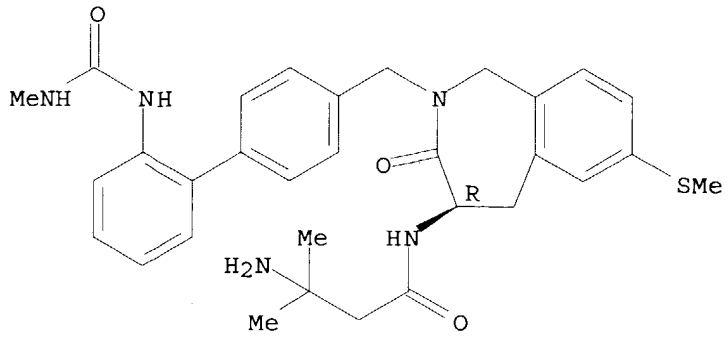
RN 168057-37-2 HCAPLUS
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-(hydroxymethyl)[1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



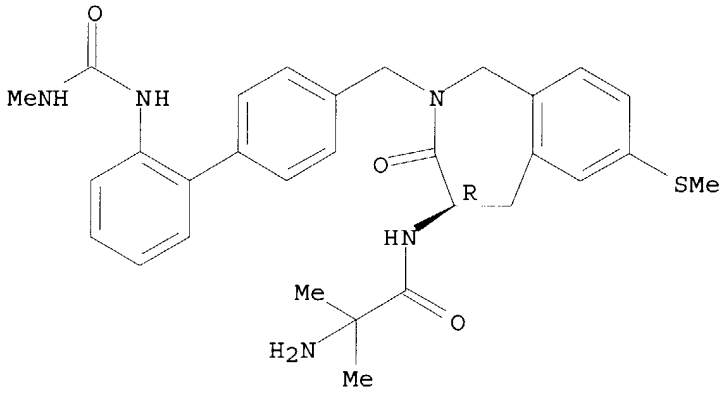
RN 168057-45-2 HCAPLUS
CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



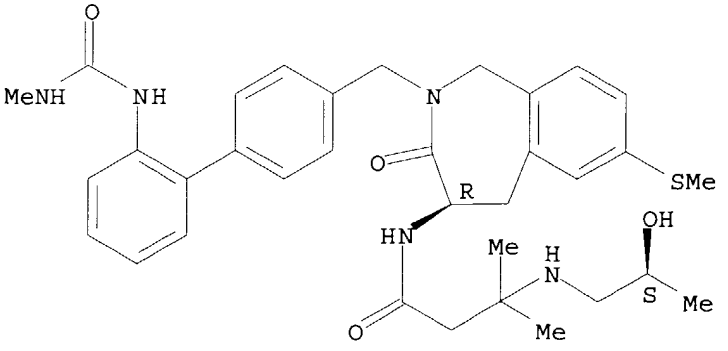
RN 168057-46-3 HCAPLUS
CN Propanamide, 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



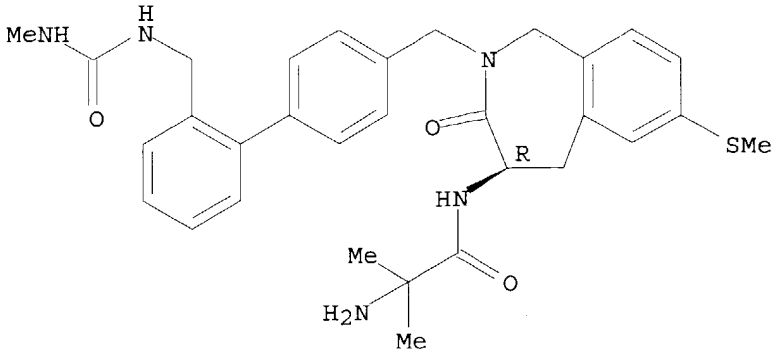
RN 168057-47-4 HCAPLUS
CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



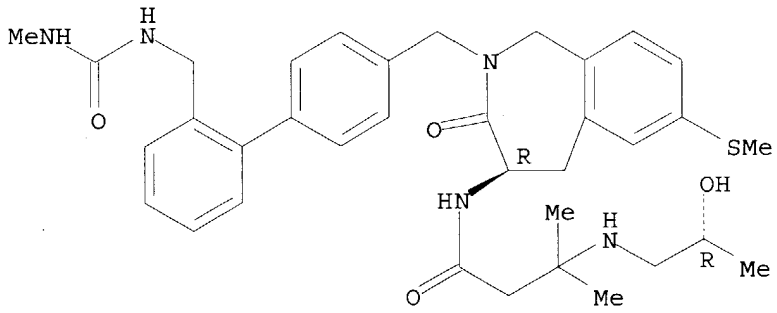
RN 168057-55-4 HCAPLUS
CN Propanamide, 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-[[[(methylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 168057-61-2 HCAPLUS
CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-[[[(methylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 168057-67-8 HCAPLUS
CN Propanamide, 2-amino-N-[2-[[2'-[[(aminocarbonyl)amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-2-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.